JUL 22 1918
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BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice

Vol. XXIX—No. 329] BALTIMORE, JULY, 1918 [Price, 50 Cents

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PREPARATION OF U. S. ARMY TRIPLE TYPHOID VACCINE[1]

By Major C. G. Snow,

Army Medical School, Washington, D. C.

This vaccine contains five strains of typhoid and paratyphoid bacilli. Of the former only the Rawlings strain, of the latter four; Rogers and Meers Para "A," and Cools and Rowlands Para "B." The Meers and Rowlands strains were secured from England and are the strains used in the English vaccine.

The preparation of vaccine on the large scale now required by the army demands many steps that are found unnecessary when only small amounts are made—steps that may perhaps appear superfluous at first but which assume vital importance when the output must run to thousands of liters monthly. In the description given below of the preparation of typhoid and triple typhoid vaccine as made in the Army Medical School, the commercialized technic required in handling this vast quantity is given with as much detail as space and time will allow.

It is hardly necessary to state that the principles and scientific facts that are commercially applied are those originally promulgated by Colonel F. F. Russell, Medical Corps, U. S. A., who may well be called the "father of typhoid vaccine"; and the most casual glance at army and navy statistics is all that is required to prove the accuracy of these principles. Following Colonel Russell came such men as Lieut.-Colonel Whitmore, Major Nichols and Major Reasoner, who devoted countless months and untiring labor that the army vaccine should go forth in any amount required with the standard unchanged. There is no doubt that time and greater experience will disclose new methods, possibly largely mechanical devices, that will greatly simplify our present technic without in any way lowering the quality of the vaccine. In fact many such devices and technical changes are at present under consideration, that are theoretically correct and practical, but in times of stress such as these we dare not introduce radical innovations in so important a process, which have not been thoroughly tested by the results they exhibit when clinically applied. For we know the success of the present vaccine and that it affords a satisfactory prevention, and we know also that under the present system it can be produced in the amounts required, so, until the times comes when a new process shall have been equally well tried we must, for the sake of our men, retain our somewhat cumbersome technic.

For the sake of description it may be convenient to divide this subject into the various sub-headings or sections used in handling this problem in the Army Medical School.

[1] Read before The Johns Hopkins Hospital Medical Society, December 17, 1917.

Preparation Department

In a general way this department is housed in three main rooms in which all the material used in the production of army vaccine is assembled and placed in proper condition. The glass-ware is sterilized, the agar made, and the cleansing of apparatus attended to. One room is devoted chiefly to hot-air sterilization, another to autoclave sterilization and the preparation of media, and the third to salt solution. Necessarily there is considerable overlapping of the duties of the men assigned to these three rooms, but as far as possible they are kept separate. All sterilization is done immediately prior to the use of the apparatus in question, and in the case of the ampoules they are always taken directly from the sterilizers to the filling and sealing room.

The medium used is ordinary nutrient agar made with Liebig's Beef Extract and Witte's peptone, the reaction being carefully adjusted to 1.0 per cent acid. The salt solution is used in 0.85 per cent strength made from chemically pure sodium chloride and distilled water. It is filtered through paper directly into one-liter flasks and sterilized in the autoclave. Following sterilization of the salt solution it is tested for sterility and never used when over 36 hours old. The agar, after preparation, is placed in Kolle flasks, 45-50 c. c. in each flask, sterilized in the autoclave and then allowed to incubate until inoculated. It is very unusual to find either agar or salt solution contaminated, for which thanks are due to those assistants who have this directly in charge.

Care of the Cultures

Three sets of three tubes each of the five cultures used in the preparation of this vaccine are kept constantly under lock and key, and only one of these is used for the routine work, the two remaining sets being kept in locations known only to the officer directly in charge. From these original cultures transplants are made, originals renewed, and working plates prepared every week or 10 days. From the stock plates individual colonies are transferred to large agar slants and double sugar tubes, the former being used to prepare the planting emulsion, and from the latter agglutinations and stains are made to test the purity of the transplanted colony. For the agglutination we use a 1 : 1000 dilution of a known serum having a titer of 1 : 5000 with a cross agglutinating index never higher than 1 : 300 and rarely this high.

In the preparation of plates, transfer of cultures, fishing of colonies, preparation of planting emulsion, and the agglutinations, the work is always done by two men, the officer in direct charge and one assistant, and a very careful double check is kept to avoid the possibility of a mistake. It is very essential that the stock plates from which transplants are made shall have distinct and clearly isolated colonies so that in subsequent utilization there can be no possible confusion.

The preliminary steps in the preparation of vaccine, which have been merely indicated, will be found to require a great many assistants and the expenditure of much time and labor, and too great emphasis cannot be laid on these stages of the process as errors here will render futile all subsequent work. The timing of these preliminary steps alone, while seemingly very simple, requires constant care and the closest application.

Inoculation of Flasks

As a routine, runs of from 2000 to 3000 flasks are made. This number, of course, requires a much larger incubating space than is supplied by the ordinary laboratory incubator and as a consequence it was found necessary to build a completely insulated room 8 ft. x 19 ft. x 12 ft. heated by 14 separate electric stove units, controlled by a thermostat and solenoid. As about 12 men are required in handling this number of flasks, and as more than six men should not be allowed to work in a room of the ordinary size, it was found necessary to establish two vaccine rooms opening directly on the incubating room. The fact that 24 hours is the minimum time required for the growth, and that the washing stage consumes about 14 hours, makes it necessary to start inoculating not later than 4 o'clock in the morning. The emulsions, however, must be prepared prior to this and it is our custom to start this process at 3 o'clock a. m. At this time the officer in direct charge and one assistant enter one of the vaccine rooms and, under as nearly as possible complete asepsis emulsify the growth from the massive agar slants above spoken of. This process is simple but requires extreme care, the slants after a thorough burning of the cotton stoppers and the mouths of the tubes are treated with about 15 c. c. of sterile broth which, after soaking for a few minutes, allows the growth to be removed by rapid rotation of the tube. This emulsion is then transferred to one or two large-sized tubes containing a similar broth, each of these tubes receiving a number designating the section it is to inoculate. Ordinarily one colony inoculates two sections, quite frequently only one, and sometimes three.

In this work a record sheet which has been previously prepared is very carefully followed (see Table 1). While this process is going on, the remainder of the assistants have entered the incubating room from another door than the one communicating with the room where the above work is being done and are burning the stoppers of the flasks *en masse*, the flame being extinguished as soon as possible with a moist antiseptic towel. During this stage the cotton stoppers are not removed. As soon as these flasks are burned other assistants stack them in wooden racks holding 50 flasks, each rack constituting one section. Half of the total number of sections desired are transferred to the unused vaccine room, by which time the emulsions are completed and the room in which this work was done is prepared for work. All who are to work in the inoculation now clothe themselves in sterile cap, gown, and rubber gloves. The inoculating apparatus consists of a small brass tube-holder with a protecting shield of antiseptic gauze, a sterile cotton swab and a Bunsen burner. The burning of cotton having been done previously, the stoppers are removed and direct inoculation made to the agar surface with the swab which is refreshened in the emulsion tube after each flask. The mouth of the flask

must be thoroughly and symmetrically flamed prior to inoculation and the greatest possible care used to contaminate neither the swab nor the emulsion tube. In this way the entire section is planted and restacked in an empty rack. The topmost flasks are marked with the section number and the inoculators' initials; the latter going also on the record sheet, thus showing by whom each section has been inoculated. When all sections

TABLE I

Run of Jan. 15-19, 1918	Strain	Section	No. flasks	Inoculator	Washer	Count	Strength	No. bottles.	Tricresol per bottle	Salt solution per bottle	Vaccine per bottle
Typhoid No. 286	Rawlings	1–30	50 50 50 50	A B C D and so on	Q R S T and so on	5500	2000	1	13.7	3500	5500
Para. "A" No. 85	Rogers	31–38	50	X Q P	Z X X	6600	3000	1	11.0	2400	4400
	Meers	39–45	50	St. Kl. Na.	Pa. Ny. Zeo.	6000	3000	1	11.5	2600	4600
Para. "B" No. 51	Coods	46–53	.. .. ..	Co. Je. ka.	Co. Pen. Gil.	6900	3000	1	11.5	2600	4600
	Rowlands	54–60	.. ..	Jk. No.	Tm. Pq.	7500	3000	1	12.5	3000	5000

are complete, they are returned in the racks to the incubating room. New swabs and emulsion tubes are used for each section.

One of the most difficult things to teach the beginner in inoculation is the necessity of covering the entire surface of the agar, which can be done only by establishing a definite method of procedure and constantly adhering to it, because, if the agar is properly prepared, the passage of the swab over it leaves no mark. In this procedure absolute asepsis is essential, rubber gloves must be worn at all times and as little movement as possible allowed in the room. Exposed agar Petri dishes are placed beside each worker to obtain a partial control of the number of air colonies near his emulsion tube.

WASHING

Under this caption we designate that stage of the process wherein the growth, after approximately 24 hours of incubation, is removed from the agar and placed in large collecting flasks for heating. Each section of 50 flasks is treated with a total of slightly less than two liters of 0.85 per cent salt solution. This is done by removing the cotton plug from an individual flask the mouth of which is well flamed, and pouring in a quantity of salt solution the amount of which must be learned by experience, so that all flasks of the section may receive a sufficient amount of solution for washing purposes without any running over the two-liter mark. The flask is then placed agar down to allow the liquid to soften the growth. All flasks of the section, after being treated as above described, are scraped, beginning with the flask first receiving salt solution. During the scraping or the removal of the growth from the agar the flasks are constantly rocked backwards and forwards, allowing the salt solution to thoroughly rinse off the growth; they are then set in an upright position in an especially designed wooden rack to facilitate draining of the emulsion from the somewhat sticky medium. The contents of these flasks are now poured into two-liter Erlenmeyer flasks designated as collecting flasks, each being marked at the two-liter level. The deficiency in volume is now made up from a sterile salt solution flask. The collecting flask is now marked with the section number and the name of the man who washed it, this same information being transferred to the record sheet. About 5 c. c. of the emulsion are now removed from the collecting flask for standardization following which the cotton stoppers are well protected with sterile tinfoil. When a sufficient number of flasks have been secured they are placed in a water-bath the temperature of which is carefully adjusted to 52.6° C. Here they are left for one hour. There are three important rules that must be followed in this stage of the process: First, be sure to remove all the growth; second, do not scrape off any agar; third, absolute asepsis.

Many different appliances have been suggested for use in removing the growth from the Kolle flasks, but we have found the one most simple and satisfactory to consist of a large platinum loop averaging from 2 to 3 cm. in diameter.

The water-bath in which the emulsion is heated was especially designed for this purpose. It consists of a circular tank in which a constant circulation of water is maintained by an electrically actuated propeller. In this bath one control flask is kept constantly with a thermometer which registers as nearly as possible the mean temperature of the vaccine emulsion.[2]

While the emulsion is being heated, standardization goes on, the counting being by the Wright system and Wright's stain

[2] Another thermometer registers the temperature of the water outside the flasks.

being employed. It has been found from experience that this technic, if properly applied, is entirely satisfactory and, inasmuch as since the beginning of vaccine preparation by the army this method has been followed, it is not deemed advisable to introduce any change, owing to the danger of altering the present standard of the vaccine. One or two rather minor points in this step are worthy of mention, the first and most important being that from the time counting is started until the completely stained slide is under the microscope, the greater the speed the more accurate the results; another is the size of the drop of blood and emulsion mixture used, which must be small enough to allow it to be completely spread over the slide so that there is no surplus. One great drawback in this method of standardization is the fact that most army men have been repeatedly vaccinated and consequently have a rather high agglutinating index. This applies to men constantly associated with the preparation of typhoid vaccine particularly, for we find from practical experience that those of us who are so associated present a very erratic and troublesome agglutination. These agglutinations on the slide frequently cause the counter many troublesome hours. In so far as possible the standardization is always done by the officer in charge, who uses his own blood with the agglutinating index of which he must of necessity become very familiar.

Culturing the Heated Vaccine

While the standardization and heating is under way, another group of assistants clean out the vaccine room and place it in proper condition for use in culturing and diluting. The two-liter collecting flasks containing the pure emulsion are then transferred to this newly prepared room and the tinfoil on the tops is removed. Tubes of melted agar, sterile Petri dishes, and pipettes are now assembled and from each of the collecting flasks under the strictest precautions, samples of the emulsion are removed and plated for purity, a portion of this sample being retained for subsequent examination should the need arise.

Diluting

The stock vaccine is carried in the following dilutions: Typhoid 2000 million per c. c.; paratyphoid "A" and "B" 3000 million per c. c. The actual strength of emulsion per c. c. for each individual flask having been determined previously by standardization, the necessary amount of salt solution to be added to make the total equal the desired strength is easily determined. Inasmuch as the vaccine is to be preserved in 0.25 per cent tricresol, the proper amount of this reagent and of salt solution is added to each of the stock bottles and thoroughly mixed. Stock bottles used for this purpose have the capacity of 8, 12, and 16 liters and are made from carefully selected glass, plugged with cotton and thoroughly sterilized in the autoclave. Prior to the addition of either tricresol or salt solution each bottle is designated by a tag bearing the number of the vaccine run, the section, strain, the date when made, and the amount and strength of the vaccine it contains. To render mistakes less likely, the tags for the different strains vary in color, typhoid being white, paratyphoid "A" yellow, and paratyphoid "B" green. Following the heating, and the preparation of the stock bottles with the proper amount of tricresol and salt solution the emulsion is poured into the stock bottles with the usual degree of care as to asepsis. Each stock bottle now contains from 3 to 7 liters of the finished vaccine which, after thorough mixing, is allowed to remain at the temperature of the vaccine room, which is approximately 105° F. at this time, for two hours. It will be seen from the above statement that each stock bottle represents one section. At the end of these two hours cultures are again made, this time including two plates and an anaërobe tube, 2 c. c. of the vaccine being used in each, and 5 c. c. placed in a sterile tube for future examination should need arise, and for animal inoculation. For the latter the vaccine is pooled and injected into mice, guinea-pigs, and rabbits. The doses used are of the same size as those given to man and in the case of the rabbit and mouse are subcutaneous and in the guinea-pig intraperitoneal, the exception being that in this last dose the quantity is 1500 million whereas the others are 500 million. A single dose only is used for the mouse and the guinea-pig, whereas 10 days after the first injection of the rabbit it receives a second dose of 500 million and 10 days following this is bled to determine the agglutinating index.

Following the plating of the tricresol-killed vaccine the mouths of the stock bottles are protected with tinfoil and returned immediately to the ice-box where they remain until the cultural and animal controls have determined their purity. This period varies, but is never less than five days and very frequently considerably longer. This step concludes the actual preparation of the vaccine, but is necessarily followed by appropriate mixing, ampouling, and testing of the final result.

Mixing

It having been decided that it was better to administer the three organisms as a single vaccine, it became necessary to mix the various strains and as a consequence convenient dilutions were decided upon as a standard for the stock vaccine. These dilutions have been noted above and allow of the typhoid and paratyphoid strains being mixed in equal volume, which from a practical standpoint greatly facilitates accuracy and speed. One part of each of the paratyphoids being mixed with four parts of typhoid gives a resultant dilution in which each cubic centimeter contains 375 million each of the paratyphoid strains and 1000 million of typhoid. This mixing is done entirely by four men, trained and trusted assistants of this department. The vaccine is measured from large stock bottles into sterile two-liter graduates, from which it is transferred to other stock bottles bearing an appropriate label for the vaccine contained. Records of this mixing are made and kept in permanent file from which it would be possible to trace back to the source any error that might arise, though the number of controls and checks that are made practically prohibit any

such accident. Following this mixing, aërobic and anaërobic cultures are made and the vaccine is not used for ampouling until after the sterility of the mixture has been definitely determined. As regards the reading of all culture control plates and tubes there is one unvarying law followed, *i. e.*, "If any doubt exists, discard the vaccine." Readings of all the culture plates and tubes are invariably made by the four men above referred to and any difference in opinion is considered sufficient evidence to warrant the discard of the vaccine resulting from the section in question.

AMPOULING

After the mixed vaccine has been released, which is never done until both the aërobic plates and anaërobic tubes have been incubated at a minimum of 24 hours, it is turned over to the ampouling department and, as in all other departments, absolute asepsis is preserved as far as possible. This work is done by men clothed in sterile cap, gown, and rubber gloves. The ampoules are taken immediately from the hot-air sterilizers to the sealing-room where they are at once filled and sealed. At no time are the ampoules, either filled or unfilled, allowed to stand uncovered. In this department also the arrangement of the vaccine into sections is strictly observed. Here one section representing one bottle that exactly corresponds in name and number with the original section planted may be traced back in case of contamination by means of the record sheet and in this way it is possible to recognize every one through whose hands it may have passed. The ampoules representing each bottle or section are packed in especially prepared cartons and three samples from each section removed for cultural examination. The packed cartons representing now the original sections are kept separate from each other until the cultural tests both aërobic and anaërobic have been determined by examination after 48 hours to be sterile. Following this the vaccine is finally released for issue. In addition to the above rather elaborate controls that have been indicated, there are others which it is unnecessary to mention.

This very brief account of army vaccine is given merely as an introduction to the motion picture illustrations of each stage of this process. Many minor points in the technic must be ignored at the present time as their description would be practically an impossibility. Difficulties are constantly arising that must be overcome, accidents occurring that must be remedied, and quick and safe judgments constantly made. We have but one rule to guide us and this we attempt to follow: "Work hard and make no mistakes."

THE INFLUENCE OF MENSTRUATION ON ACIDOSIS IN DIABETES MELLITUS. REPORT OF A CASE[1]

By GEORGE A. HARROP, JR., and HERMAN O. MOSENTHAL

Menstruation has not been regarded as a factor which influences the course of diabetes mellitus appreciably. Naunyn[2] quotes Lecorché as claiming that menstruation has a tendency to diminish glycosuria. Naunyn's own experience evidently points in exactly the opposite direction. We have not been able to find any allusions to the effect that menstruation may have on acidosis. The report of the present case is of interest in this connection. The history and the physical examination of this patient were as follows:

H. L., Medical No. 38691.—Colored; aged 18; schoolgirl. Admitted September 21, 1917. Discharged November 11, 1917. Died November 27, 1917.

Family History.—Not important.

Past History.—Essentially negative. Menstruation began at 15. The periods were regular, but often lasted for a week. They were accompanied by a good deal of dysmenorrhea. Her best weight before onset of the diabetes was 101 pounds.

Present Illness.—The first definite symptom of diabetes was polyuria, which was noticed one year ago and has gradually become more marked, until now she voids every hour or two during the day and night. At about the same time she began to lose weight, and to feel drowsy and listless. She grew irritable and complained of pains in the legs, and later in the back. Her appetite has become enormous and she has had excessive thirst. During the past few months her menses have become more irregular. The last period occurred about two weeks prior to her admission and lasted a week. During the last three or four days of menstruation, the mother states, the girl was very drowsy, she had no desire for food, she complained of abdominal pain, her breathing was deep, and the amount of urine voided during this time was much less than usual.

Physical Examination.—Height 5 feet 1½ inches. Weight 72½ pounds. A thin, undernourished colored girl. The pupils are equal and react to light. Marked pyorrhea alveolaris. Heart and lungs clear. Abdomen negative; liver and spleen not enlarged. Thyroid isthmus palpable, and contains a pea-sized nodule. Knee-jerks absent. There are no motor or sensory disturbances.

Blood Examination.—W. B. C., 7900. R. B. C., 5,200,000. Hemoglobin (Sahli), 78 per cent. Wassermann reaction negative. Blood sugar on admission, 0.148 per cent.

Throughout these studies the nitrogen was determined by the Kjeldahl method, the urinary ammonia by Steel's modification of Folin's method,[3] the urinary glucose of Benedict's modification of Fehling's solution,[4] the acetone substances in the urine by Shaffer's[5] procedure, the blood sugar by the method of Lewis and Benedict,[6] the tension of carbon dioxide

[1] From the Medical Clinic of The Johns Hopkins Hospital.

[2] Naunyn, B.: Der Diabetes Mellitus. Wien, 1906, p. 235.

[3] Steel, M.: Jour. Biol. Chem., 1910, VIII, 365.

[4] Benedict, S. R.: Jour. Am. Med. Assn., 1911, LVII, 1193.

[5] Shaffer, P. A.: Jour. Biol. Chem., 1908, V, 211.

[6] Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, XX, 61.

in the alveolar air according to Marriott,[1] and the food values were calculated from the tables of Atwater and Bryant.[2]

From Table I, it is readily appreciated that this girl entered the hospital suffering from a very severe type of diabetes mellitus, accompanied by a marked degree of acidosis. The urine could be rendered sugar-free only temporarily by means of starvation; the acid substances in the urine were fairly high, the percentage of ammonia nitrogen of the total urinary nitrogen was well above the normal, and the carbon dioxide tension of the alveolar air was low, in spite of the large amounts of bicarbonate of soda administered. The patient was thin and weak, but exhibited none of the distressing subjective symptoms that are often associated with marked acidosis and impending diabetic coma. The gravity of the situation was realized, and every effort was made to improve the girl's condition. At the end of one month, the acidosis had somewhat diminished, but the tolerance for carbohydrates had not increased at all. She was evidently one of the rare but unfortunate cases of diabetes mellitus which are not relieved by the starvation treatment.

On the 28th of October, with the onset of the menstrual period, the picture changed completely. On that day she complained of abdominal pain and refused food. At 7 p. m. a change in the character of the breathing, with increasing drowsiness, was noticed, and at 10 p. m. there was well-marked hyperpnea; she could scarcely be aroused; there was marked involuntary twitching of the facial muscles, and the carbon dioxide tension of the alveolar air was 20 mm.

The next day the symptoms remained unchanged. On the third day the conditions improved somewhat and by November 1 all the symptoms which had manifested themselves at the time of menstruation began had disappeared. The patient was treated with large doses of bicarbonate of soda by mouth, rectum, and intravenously, and by starvation. The effects of this therapy were satisfactory.

The tests during this period, which may be regarded as one of diabetic coma, show no appreciable increase in the severity of the acidosis over that of one month previously when there were no subjective symptoms of acidosis. There is perhaps a slight tendency toward a rise in the amount of acid substances and ammonia, but no significant change occurred.

The alveolar air showed a lower tension of carbon dioxide on the first day of menstruation than had previously been recorded, but here again the difference was only slight. It may,

TABLE I

DATA FROM A CASE OF SEVERE DIABETES MELLITUS. THE SYMPTOMS OF ACIDOSIS WERE MOST MARKED AT THE BEGINNING OF THE MENSTRUAL PERIOD

Date	Urine						Alveolar CO_2 Mm. Hg.	$NaHCO_3$ by mouth Gm.	Food					Remarks
	Glucose	Reaction	Acetone bodies as B.-Oxybutyric ac. Gm.	N Gm.	NH_3 Gm.	NH_3 Coefficient			Protein Gm.	Fat Gm.	Carbohydrate Gm.	Alcohol Gm.	Total calories	
9-23-17	36.5	Ac.	....	7.74	2.14	22.9	23	96	4	0	4	0	33	During this period the patient was subjectively well; there was no hyperpnea, drowsiness or other symptom that might be referred to acidosis.
9-24-17	+	Ft. ac.	....	....	....	....	38	96	27	12	5	0	243	
9-25-17	28.1	Ac.	79.7	8.58	3.50	34.0	..	48	37	53	4	0	661	
9-26-17	24.3	Ac.	39.9	8.37	3.38	37.0	25	24	55	43	8	0	658	
9-27-17	Trace	Ac.	14.0	4.62	2.37	42.4	25	24	10	1	0	19	183	
9-28-17	0	Ac.	19.2	4.77	1.88	34.8	23	24	18	11	7	19	338	
9-29-17	1.2	Ac.	8.0	2.00	0.92	38.0	23	24	40	31	12	0	404	
9-30-17	Trace	Ft. alk.	....	2.72	0.99	30.2	31	24	14	14	0	0	188	
In the interval the patient was kept on a diet varying between starvation and 1500 calories of carbohydrate-free food. The urine was never sugar-free, excepting as the result of starvation. The carbon dioxide tension of the alveolar air varied between 23 and 36 mm. of mercury. Except for the presence of acetone bodies in the urine, there were no further signs or symptoms of acidosis noted.														
10-28-18	24.8	Ac.	39.2	9.28	3.90	34.6	20	12	3	0	0	0	12	First day of menstrual period; marked hyperpnea, extremely drowsy, very restless at times, twitching of facial muscles.
10-29-17	22.5	Ac.	56.4	13.73	2.03	12.2	25	88*	4	0	0	0	16	Hyperpnea, drowsy, nauseated.
10-30-17	16.2	Ac.	43.3	12.73	3.93	25.4	29	56	12	7	0	0	114	Brighter; breathing normal; still very drowsy.
10-31-17	25.4	Ft. alk.	49.0	12.00	4.50	31.0	36	48	39	31	7	0	478	Considerably brighter.
11- 1-17	17.7	Ac.	54.7	8.47	3.53	33.3	..	32	38	21	10	0	392	Normal.
11- 2-17	6.8	Ac.	22.3	5.54	2.83	42.0	..	16	13	1	0	39	336	
11- 3-17	15.3	Ac.	29.7	8.04	3.15	32.3	..	16	45	35	12	0	559	
11- 4-17	16.3	Ac.	34.4	8.09	4.02	41.0	..	16	15	1	0	39	344	
11- 5-17	11.6	Ac.	32.9	6.75	2.76	33.8	..	16	15	1	0	39	344	
11- 6-17	10.6	Ac.	24.5	7.36	3.07	34.5	..	16	15	1	0	39	344	
11- 7-17	5.6	Ac.	16.9	4.92	1.96	32.9	..	16	15	1	0	39	344	
11- 8-17	14.0	Ac.	28.4	16.89	3.09	15.1	..	16	71	72	12	39	1283	
11- 9-17	9.8	Ft. alk.	24.4	7.12	2.93	34.0	..	16	52	65	12	39	1140	
11-10-17	8.9	Ac.	32.6	6.89	2.24	26.8	..	16	50	31	12	13	634	
11-11-17	7.3	Ac.	27.8	6.40	2.42	31.3	..	16	31	32	12	13	485	
11-12-17	17.1	Ac.	25.1	6.77	1.86	23.0	..	16	46	31	12	13	617	

* Besides sodium bicarbonate by mouth, 25 gms. were given by intravenous injection and 30 gms. by rectum.

[1] Marriott, W. McK.: Jour. Am. Med. Assn., 1916, LXVI, 1594.

[2] Atwater and Bryant: U. S. Dept. of Agriculture, Bull. No. 28, 1906.

FIG. 1.—Left hand.

FIG. 2.—Right hand.

FIG. 3.

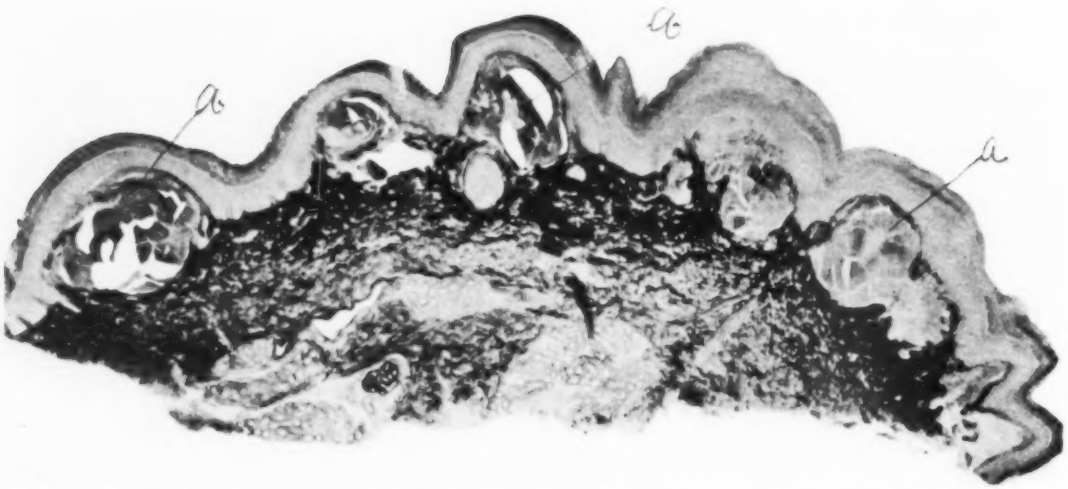

FIG. 4.—Weigert's elastic tissue stain, showing masses of colloid material in papillary layer of the cutis *a*, *a*, *a*.

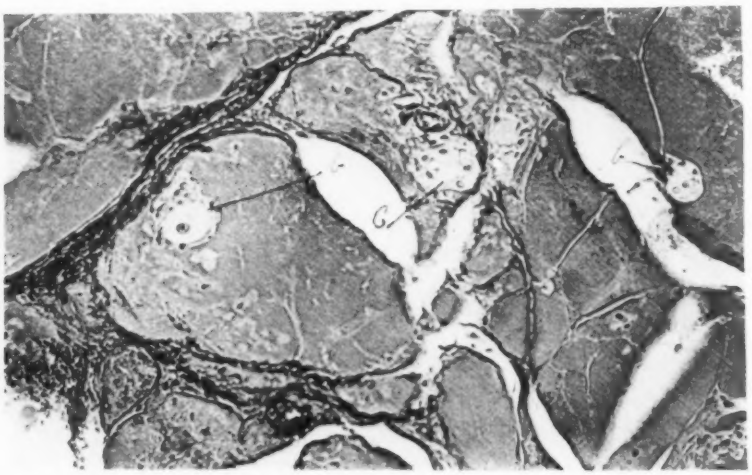

FIG. 5.—Enlargement of small area within one of the colloid masses (fig. 4, *a*). *b*. Large cells with granular protoplasm. *c* shows gland-like arrangement of these cells.

therefore, be concluded that the process of menstruation in some manner affected the body so that it was less resistant to the influences of the acid bodies and that diabetic coma resulted.

There are several other facts that point to the profound effects which were produced by the menstrual process. During the period the glycosuria and the quantity of nitrogen in the urine were both much increased. These phenomena have often been noted in so-called cases of acute diabetes. When menstruation had ceased, it was apparent that some permanent damage to the carbohydrate metabolism had occurred. The amounts of glucose excreted were somewhat higher than before, and the acidosis, as indicated by the acetonuria and the quantity of ammonia in the urine, was distinctly more pronounced.

Letters received from the patient's mother and her physician would seem to show that during the two weeks after she left the hospital (November 11) her condition was thought to be unchanged. She was permitted to be up and about and there was presumably very little restriction imposed upon her diet. On November 25 menstruation began. She was very drowsy and nauseated. Deep coma came on during the course of the day, and on the following day several general convulsions occurred. There was evidently typical air hunger. Death came about 36 hours after the onset of the diabetic coma, and on the third day following the beginning of the menstrual period.

In this case of diabetes mellitus it seems justified to conclude that the menstruation was accompanied by an increase in the acidosis. The symptoms became more marked with each successive period until fatal coma occurred. This is not a common sequence of events, but may possibly be regarded as an indication that diabetic patients should be closely observed during the menstrual period.

A CASE OF COLLOID DEGENERATION OF THE SKIN WITH AN UNUSUAL HISTOLOGICAL FEATURE

By LLOYD W. KETRON, M. D.

(From the Dermatological Department of The Johns Hopkins University)

Colloid degeneration of the skin was first described in 1866 by Wagner, who gave it the misleading name of *colloid milium*. It is a very rare disease. According to Hartzell[1] only 22 cases have been recorded and in a relatively large number of these the correctness of the diagnosis is open to question. Arzt[2] claims that in only 10 of the reported cases was the diagnosis definitely confirmed by histological examination.

The following example of this disease is reported in order to put the case on record and also emphasize an unusual histological feature:

The patient was a Virginian, aged 42, single, and a carpenter by trade. He had had no serious illnesses and his general health had always been good. He chewed tobacco, but did not smoke nor use alcoholic drinks. In his work he was not in the habit of handling paints, oils or chemicals.

The disease had begun (as the patient described it) 12 years before, with the appearance of a "little patch of warts" on the back of the left hand just behind the knuckle of the forefinger. Very soon afterwards the back of the right hand had become affected, and the eruption had very gradually reached its present extent. The ear had been implicated for about five years. There had been no subjective symptoms.

On examination, the process was found to be limited to the backs of both hands and the helix of the left ear (Figs. 1, 2 and 3). It extended on to the first phalanges of some of the fingers, but the palmar surfaces were not involved. On the hands the eruption consisted of a thick aggregation of papillomatous lesions somewhat larger or smaller than a pinhead and with an elevation of 1 or 2 mm. They were round, oval or triangular in shape, and occasionally semiglobular ones with restricted bases were found. The surfaces of most of the lesions were smooth, flat, and frequently had a glazed appearance. In the center they were brownish- or reddish-yellow in color and appeared to contain fluid. One of them was pricked with a needle but no fluid escaped. The whole top was then pulled off and a jelly-like, friable, brownish-yellow substance was disclosed, embedded in the skin. It was easily expressed, leaving an opening which rapidly filled up with blood.

On the ear (Fig. 3) the disease extended along the helix, forming a protuberance about 3 cm. long and 3 or 4 mm. high. Here the lesions did not form separate elevations as on the hands, but a diffuse thickening with a more even surface was formed, within which could be seen the brownish or yellowish masses embedded in the skin.

No other dermatological condition was noted except a large number of black comedones over the nose, cheeks and forehead.

Histological Examination.—A piece of tissue was excised from the back of the hand and the sections stained with: (1) hematoxylin and eosin; (2) picric acid and fuchsin; (3, 4) Weigert's elastic tissue stain combined with (a) safranin and (b) hematoxylin; (5) acid orcein; (6) polychrome methylene-blue.

No change was noted in the epidermis except a flattening out of the interpapillary pegs.

In the papillary layer of the cutis, round or irregular masses of a homogeneous material were found, which had raised the epidermis up into the papular elevations noted in the clinical descriptions (Fig. 4). These masses were not confluent and were rather sharply separated from the surrounding colla-

[1] Colloid Degeneration of the Skin with Report of a Case of So-Called Colloid Milium. The Journal of Cutaneous Diseases, 1914, XXXII.

[2] Zur Kenntnis des "Pseudo-Milium colloidale." Arch. f. Dermat. u. Syph., 1914, CXVIII.

genous and elastic tissues. They were divided up into irregular blocks by branching lines which appeared as a simple break or consisted of one or more strands of connective tissue, in which were well-preserved nuclei and occasionally small blood-vessels (Fig. 5). (The fixation, staining and manipulation of the sections have resulted in a noticeable separation of many of the blocks.)

The most striking thing observed in the histological study were peculiar cells with round or oval vesicular nuclei, apparently embedded in the colloid blocks or lying along the connective-tissue strands between them (Fig. 5). They were comparatively scarce, but a few of them were found in all of the sections. They occurred singly or in groups and in one instance surrounded an opening in glandular fashion (Fig. 5, *c*). Their size varied from that of a small lymphocyte to that of one 4 or 5 times as large. The protoplasm, especially of the larger cells, was abundant and filled with granules which took the stains somewhat as did the colloid material, although much more faintly. These cells frequently appeared as if they had been carved out of the surrounding colloid material. Pseudopodia-like processes were occasionally present. Many of them, however, were not so striking in appearance and differed in no way from the connective-tissue cells except that there were a few granules in the protoplasm. Most of the cells apparently contained only one nucleus, but frequently they lay together in such a manner that their outlines were not well defined.

The elastic tissue in the upper half of the corium was partly swollen and degenerated and a narrow fringe lay between most of the colloid masses and the epidermis.

I was unable to follow the formation of the colloid from collastin, or to find the large amounts of collacin as described by Unna.[3] The lines of division between the collagenous and elastic tissues, on the one hand, and the colloid masses, on the other, were on the whole rather sharply defined.

No definite colloid changes were found in the blood-vessels of the corium, the sweat glands or epidermal cells.

The only unusual feature which the histological study has brought out are the peculiar cells which lay in the colloid masses. These have apparently been mentioned by only one investigator, Bizzozero.[4] Although he does not speak of the granular nature of the protoplasm, I presuppose them to be cells similar to those I have seen. He describes them as containing large vesicular single or multiple nuclei and a more or less distended (*geblätes*) rich protoplasm with narrow processes. The author believes that they originate from endothelial and connective-tissue cells.

I was especially interested in these cells because they reminded me of those described by Dr. Gilchrist and myself in a case of fatty atrophy of the skin.[5] (In this case, however, the granules were represented in the sections only by vacuoles, since the fixative agent had dissolved out the granular material.) We showed that these cells were macrophages which had taken up the fat probably because some chemical change had converted it into a foreign body.

I believe the process is similar in the case of colloid degeneration of the skin, and that these peculiar cells are macrophages or cells which have phagocytosed the colloid material in an attempt to remove it from the tissues. The cells of this type are usually derived from connective-tissue and endothelial cells. In our case, they have most likely been formed from the well-preserved connective-tissue cells which were present in the colloid masses.

Conclusions.—A typical case has been reported of the rare condition of colloid degeneration of the skin. In the histological study, peculiar cells with granular protoplasm were found embedded in the colloid blocks. These have apparently been described by Bizzozero, but he did not recognize their nature or function, if my conception of them is true. I believe them to be macrophages which have phagocytosed the colloid material, because of its foreign body reaction.

I wish to thank Dr. Gilchrist for permission to publish this case.

[3] Histopathology of The Diseases of the Skin (English translation), 1896.

[4] Ueber eine klinisch ganz eigenartige Form von Pseudo-Colloid-milium. Arch. f. Dermat. u. Syph., 1910, XCV.

[5] A Unique Case of Fatty Atrophy of the Skin, etc. The Johns Hopkins Hospital Bulletin, 1916, XXVII.

A SARCOMA OF THE UTERUS ARISING FROM THE ENDOMETRIUM

By Leo Brady, M. D.

(*From the Gynecological Department of The Johns Hopkins Hospital*)

Gyn. No. 23234.—S. F., aged 53, entered The Johns Hopkins Hospital, on Dr. Cullen's service, July 23, 1917, complaining of slight uterine bleeding and of a small lump in her left breast. The breast condition gave the patient more concern than did the bleeding.

Her family and previous histories were negative. The patient had been married 31 years and had had three children. These were living and well. The labors were spontaneous and not difficult, and there was no later trouble. The patient had ceased menstruating several years before, but for the last six months had been having some bloody discharge from the uterus. This was very scanty in amount. When she entered the hospital her chief complaint was of a small lump in the left breast, which she had noted for some time.

On pelvic examination the outlet was found to be moderately relaxed, the cervix normal in consistency, not enlarged. The uterus was about twice the natural size, regular in outline and freely movable. No pelvic tenderness was made out.

FIG. 1.—Sarcoma arising from the endometrium of the uterus. Endometrium normal everywhere except at the left cornu where the growth is attached. Tubes and ovaries normal.

FIG. 2.—Low-power picture. In the upper part of the microphotograph we find normal uterine muscle. The junction of the mucosa with the muscle is sharply defined. The endometrium contains a few glands, but the greater part of the tissue is made up of large irregular cells of the sarcoma.

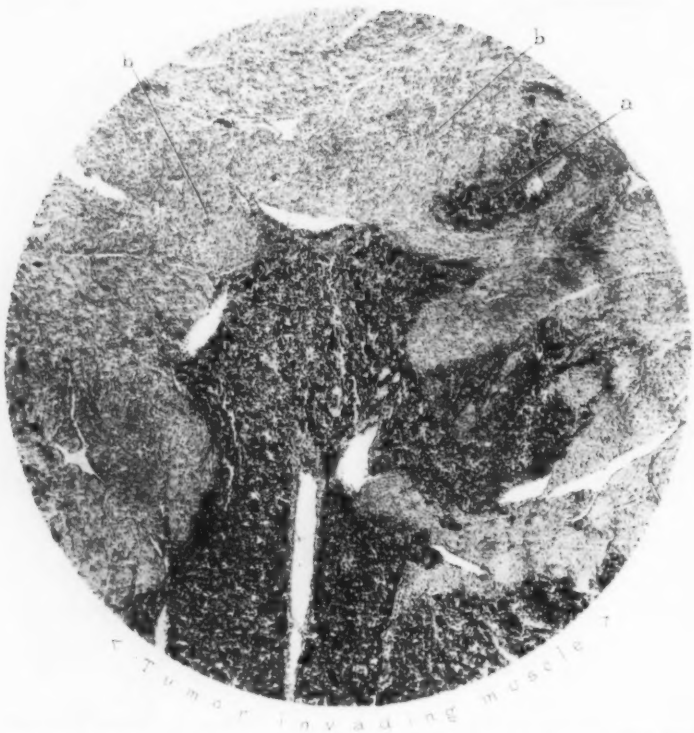

FIG. 3.—Low-power picture. The dark areas are sarcomatous and one can readily, even with the low power, make out large black masses of pigment in sarcoma cells. *a* marks an island of tumor cells surrounded by normal uterine muscle (*b*).

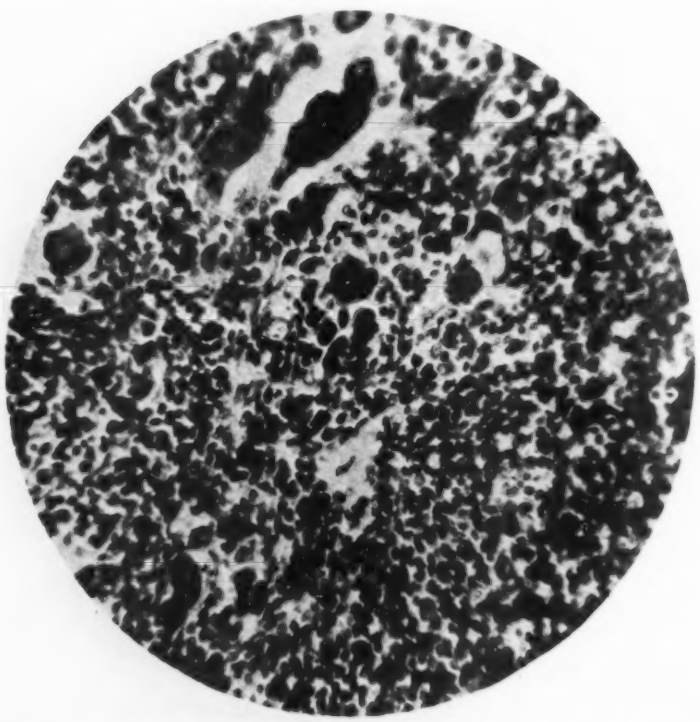

FIG. 4.—Characteristic appearance of the growth with the high power. The cells, as a whole, are fairly uniform and have uniform and deeply staining nuclei, but here and there are large irregular masses of pigment.

Operation.—On July 25, 1917, Dr. Cullen dilated and curetted the uterus and obtained a considerable amount of material. While frozen sections of the curettings were being made the breast nodule was examined. This nodule was about 1.5 cm. in diameter It was removed and was found to be a simple cyst. By this time the scrapings had been examined. The frozen sections showed the typical picture of a round-cell sarcoma.

The cervix was then sewed up to prevent any of the sarcomatous material from escaping during the abdominal operation. The entire uterus and both tubes and ovaries were removed.

On the day following operation, the patient was in good condition, but on the afternoon of the second day her temperature ran up to 104° F. Her general condition, however, was good and there was no abdominal distention. On the third day she was in good condition, but on the fourth day her temperature rose to 105° F. As the patient came from Canada and from a location where one would not suspect malaria this was not at first thought of, but it was learned that she had just been visiting some friends along the Potomac. Examination of the blood showed both sexual and asexual forms of the malarial parasites. Under quinine therapy the infection cleared up and on August 17 the patient was discharged in excellent condition. She was heard from again on November 1, 1917, when she wrote that she had no symptoms in any way suggesting a recurrence of the growth.

Gyn. Path. No. 23234.—The specimen consists of a uterus with both tubes and ovaries attached, the entire mass weighing 140 grams. The uterine cavity measures 8 cm. in length. When the uterine cavity was opened, there was seen a heart-shaped growth attached to the upper part of the fundus near the left cornu. The growth measured 4 x 5 x 4 cm. and felt quite soft. In fresh section the cut surface was homogeneous; the color white, mottled, with light yellow. Several large venous sinuses stood out plainly. The uterine mucosa seemed normal everywhere except at the point where the tumor had arisen. The tubes and ovaries and cervix were perfectly normal and careful measurements showed them not to be enlarged. There were no adhesions around the uterus, tubes or ovaries.

Fig. 1 shows very clearly the heart-shaped growth arising from the endometrium near the base of the fundus; the rest of the endometrium and the tubes and ovaries appear to be normal. Sections taken from the cervix, tubes and ovaries show no invasion of these tissues by the growth.

The microphotographs (Figs. 2, 3 and 4) are from frozen sections through the growth and uterus at the place of attachment of the growth and fundus.

At the top of Fig. 2 the letter *b* denotes the uterine muscle, which shows no signs of myomatous change. Below this we have a region (*a*) in which we find remains of the uterine glands. At the bottom of the picture we have only tumor cells.

Fig. 3 shows the tumor cells invading the muscle tissue. It is to be noted here, also, that even at the point where the tumor and muscle tissue come together there are no myomatous changes. At *a* is an island of tumor cells surrounded by normal uterine muscle (*b*).

Fig. 4 shows a high-power field taken from the sarcoma itself and demonstrates the extremely cellular character of the growth and the masses of deeply staining cells.

This case is interesting principally because it is an example of the importance of paying attention to any menstrual irregularity in women of the cancerous age. Here we have a woman entering the hospital worried because of a lump in her breast which turns out to be, on operation, a benign tumor, but paying little attention to the recurrence of vaginal bleeding, one and a half years after the menopause, which scrapings demonstrated to be due to a very malignant growth.

Finally, the case is interesting because we are apparently dealing, not with a sarcoma starting from a malignant degeneration of a fibroma, as is usually the case, but with one arising from the connective tissue of the endometrium. Certainly we find no myomatous changes anywhere, and on examining the sections one cannot help but be struck by the fact that the tumor cells have arisen from the region where we find the remains of the uterine glands. Such tumors, while occasionally reported, are nevertheless quite rare.

I wish to extend my thanks to Mr. Max Brödel and to his pupil, Miss Ethel Norris, who made the excellent drawings of this tumor.

A PHARMACOLOGICAL APPRECIATION OF SHAKESPEARE'S HAMLET: ON INSTILLATION OF POISONS INTO THE EAR

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Shakespeare's works abound in references to drugs and poisons; some of these pertain to the mystic vagaries and superstitions of kakopharmacy or dirt medicine, alchemy and witchcraft; others, on the other hand, are borrowed from the more scientific, even though empirical, data furnished by the materia medica and poison-lore of antiquity and the Middle Ages. In the present paper I have attempted to analyze and discuss in the light of modern science a passage in Hamlet which is of extreme interest to the student of medical history from the pharmacological and toxicological points of view. I am refer-

ring to the manner of Hamlet's father's death as described by his ghost in Act I, Scene 5, lines 59 to 73. The passage in full reads as follows:

> "Sleeping within mine orchard,
> My custom always in the afternoon,
> Upon my secure hour thy uncle stole,
> With juice of cursed hebenon in a vial,
> And in the porches of mine ears did pour
> The leperous distilment; whose effect
> Holds such an enmity with blood of man
> That swift as quicksilver it courses through
> The natural gates and alleys of the body:
> And with a sudden vigour it doth posset
> And curd, like eager droppings into milk,
> The thin and wholesome blood: so did it mine;
> And a most instant tetter bark'd about,
> Most lazar-like, with vile and loathsome crust
> All my smooth body."

The points of interest to us as medical men in connection with these lines are: Firstly, what is meant by the poisonous hebenon, or hebona as it appears in some editions? Secondly, what were the properties of that poison as known to Shakespeare? Thirdly, what do we know of the poison in the light of modern toxicology? Fourthly, how common was the method of instillation of poisons into the ear in ancient and medieval times? And lastly, what does modern pharmacology teach us as to the possibility of absorption of drugs and poisons through the intact ear? I may say at once that all of the above points with the exception of the last have been more or less discussed by Shakespearean scholars. I have, however, not been able, even after a most laborious search through the literature, to find any information as to the possibility of absorption of poisons through the intact ear. This fact has led me, in connection with this historical research, to undertake an experimental investigation on the subject, especially as I have during the past year been engaged in the study of absorption of pharmacological reagents through devious and unexpected channels, the results of which have partly already been published.

Variations in Readings

Two different readings for the poisonous plant employed by Hamlet's uncle in the murder are found in different editions of the play. In the first edition of Hamlet, the Quarto of 1603 (Q_1), we find:

> "With juyce of Hebona
> In a viall."

In the Quarto of 1604 (Q_2) and in all the subsequent quartos (Q_3, Q_4, Q_5 and Q_6) the reading is also Hebona, as follows:

> "With juyce of cursed Hebona in a viall."

In the Folio of 1623 (F_1) and in subsequent folios, on the other hand, the reading is hebenon, as quoted above, and this reading is followed by all subsequent editions of Hamlet. It is thus seen that two different words, *hebona* and *hebenon* are employed for the poisonous plant used by the murderer. What these words mean, whether the two words are but different terms for the same plant or whether the two refer to two different kinds of poisons and what these poisons were, has been a bone of contention among Shakespearean students for many years.

Hebona or Hebenon

Various explanations of these words are given by different scholars. I have found altogether five interpretations: some holding that hebona or hebenon means the yew-tree; others that it refers to henbane or *hyoscyamus niger;* still others explain it as *ebony;* a few suggest that the word may refer to hemlock; and a few others think that the deadly nightshade or belladonna is here meant.

Thus Grey[1] says, "Hebenon stands by metathesis, for henebon, that is, henbane, of which the most common kind, *hyoscyamus niger* is certainly narcotic, and perhaps, if taken in considerable quantity, might prove poisonous." Singer[2] says: "The French word *hebenin* applied to anything made from ebony comes indeed very close to the hebenon of Shakespeare." Elze[3] suggests: "Perhaps should we not conjecture that hemlock was intended here?" Beisley[4] states, on what grounds it is not clear, that "Hebenon might have been originally written *cucron*, one of the names common at that time for *solanum maniacum*, called also the deadly nightshade." Tschischwitz[5] says: "Hebona can be only a mistaken substitution of the Spanish and Italian *ebano*, the French *ébène* and the Latin *ebenus* and *hebenus*, all of which mean ebony. Nicholson[6] and Harrison,[7] on the other hand, both of whom are profound Shakespearean scholars, adduce some very good evidence that hebona is the original reading and that it refers to the yew-tree, well known to the ancients for its poisonous properties. A review of all the evidence on the subject leaves only two explanations of the word worthy of consideration: that of hebona, meaning the yew-tree, and that of hebenon as a corruption of the word henbane.

Concerning Heben, the Yew-Tree

There is a great deal of evidence in favor of the hebona of the quarto texts of Hamlet as having reference to the English yew-tree or *taxus baccata*. Though the form hebona is somewhat unusual, the word *hebon* is not uncommon among other Elizabethan writers. Thus in Marlowe's Jew of Malta, Act III, Scene 4, we find:

> . . . . "The blood of Hydra, Lerna's bane
> The Juice of Hebon, and Cocytus' breath."

where hebon is generally taken for *heben*, the yew-tree, branches of which were much used by archers in old England for making their bows. In Spenser's Faerie Queene, we find the following verses:

> "Lay now thy deadly Heben bow apart" (I, Pr. 3, 5).
> "His speare of heben wood behind him bare" (I, vii, 37, 2).
> "Trees of bitter gall and Heben sad" (II, vii, 52, 2).
> "Heben lance and covered shield" (II, viii, 19, 6).

The yew-tree, *taxus baccata*, has borne the reputation of being poisonous from remote antiquity. Dioscorides, speaking of the juice of green yew leaves, writes that it speedily produces death.[8] Pliny speaks of it as "taxus tristis et dira,"[9] and adds that drinking-cups made from this tree were found

to impart a deadly property to the wines drunk out of them. Statius,[10] Lucretius [11] and Plutarch,[12] all describe the taxus or yew-tree as being poisonous. "Metuendaque succo taxus," says the first of these; "the juice of the yew is to be feared." Nicholson indeed points out that Shakespeare's expression, "cursed hebona" and "holds such enmity with blood of man," may have been suggested by Pliny's description of the plant. Spenser's epithet of "deadly" applied to the heben bow must also refer to the poisonous properties of the yew. Shakespeare himself mentions the yew-tree four times in his plays and in every case connects it with death or some sad event. Thus in Twelfth Night, Act II, Scene 4, line 55, we read:

> "My shroud of white, stuck all with yew,
> O prepare it."

In Titus Andronicus, Act II, Scene 3, line 107, we read:

> "But straight they told me they would bind me here,
> Unto the body of a dismal yew."

In Macbeth, Act IV, Scene 1, line 27, the witches howl:

> "Slippes of yew
> Silvered in the moon's eclipse."

And in Richard II, Act III, Scene 2, line 113, we find:

> "Learn to bend their bows
> Of double fatal yew."

The expression "double fatal" in the last quotation refers evidently to the poisonous properties of the yew in addition to its being a weapon of warfare. All the citations given above certainly point to the prevalence of the belief in Shakespeare's times that the yew-tree was poisonous and may have well suggested to him its use in the play. Let us now inquire into what modern toxicology can tell us concerning the properties of *taxus baccata*.

On the Toxicology of Taxus Baccata

If we examine scientifically the literature on the subject of yew poisoning we shall be surprised to find abundant evidence as to the poisonous nature of the plant. Not only the berries but also, and to a greater degree, the leaves and the bark of *taxus baccata* have proved poisonous. The ancient authorities on the subject have already been cited; a considerable number of cases of poisoning are described by modern writers. Thus Falk [13] has collected 32 cases of poisoning by *taxus baccata*, nine of which resulted from eating of the red berries and 23 from the swallowing of infusions of the leaves. Twenty of the patients died, making the percentage of fatal cases 62½ per cent. Hurt [14] reported the death of a child of three and a half years who swallowed a quantity of yew berries. New [15] reported a case of poisoning in an insane patient who swallowed a large quantity of them. Taylor [16] reports two cases of severe yew poisoning. Heffter [17] describes a fatal case of poisoning in an adult; and other cases may be found cited in the toxicological reference works by Kobert,[18] Kunkel [19] and Blyth.[20]

The leaves of the yew were not infrequently employed to induce abortion.

The chemistry of *taxus baccata* has been studied by the French toxicologist Marmé,[21] who isolated an active principle with alkaloidal properties which he named *taxin*. This is an amorphous white powder having the empirical formula $C_{37}H_{52}NO_{10}$, soluble in alcohol, ether and chloroform, insoluble in benzene and slightly soluble in water. The substance melts at 82°C. and gives an intense purple-red color with H_2SO_4 and a reddish-violet color with Frochde's reagent. The salts of taxin are freely soluble in water. Lewin [22] gives the lethal dose of taxin for frogs as being from 50 to 70 mgms., and for cats as being from 30 to 50 mgms. The lethal dose for man is not given, but death has been reported to occur rapidly after swallowing large quantities of the infusion from leaves in from one and a half to twenty-four hours. The chief experimental work on yew poisoning has been done by Borchers,[23] who found that death was produced primarily through respiratory paralysis. Taxin, however, was found by him also to be poisonous to the heart and to the central nervous system. Concerning the pathological findings in fatal cases, there is nothing characteristic reported by reliable pathologists, the only constant lesion being an intense inflammation of the intestines.

On the Relation of the Word Heben to Ebony

Mention has already been made of the hypothesis advanced by some Shakespearean students that hebona might really refer to the ebony tree. It therefore behooves us to inquire whether the ebony tree or *diospyros ebenus* of India is poisonous or not. There is no evidence in the literature ascribing to the ebony tree any poisonous properties. Among modern authorities the most complete account of the medicinal properties of the ebony tree is by W. Ainslie.[24] This writer states that the juice of the ebony is perfectly innocuous, and that it is used by the natives as a remedy for certain complaints of the liver and in cases of dysentery. Shakespeare, therefore, could hardly have used the word *hebona* to mean the ebony tree.

The confusion of hebona with ebony, however, is interesting from the etymological point of view. The English word heben, yew-tree, is really the same word as ebony applied to the *Diospyros ebenus*. The Greek ἔβενος, the Latin ebenus, the Italian and Spanish ebano and the French ébène, all names for ebony, all come from the original Hebrew root *eben*, which means a stone, and refer to the hardness of ebony wood and not, as may be at first glance supposed, to its color. Nicholson and Harrison call attention to the fact that in the Middle Ages the word ebenus or ebony was applied to any hard wood, and thus it came to pass that the same term was used to mean also the yew-tree, the wood of which is remarkable for its hardness. Thus arose the Scandinavian and high and low German words *Eben*, the Dutch Iben, the Swedish Eben, the modern German Eibe(n) and the Danish Heben, a form which is also found in Elizabethan literature.

Concerning Hebenon and Henbane

Whereas the advocates of the yew-tree theory regard the reading *hebenon* of the Folios as a misprint for the earlier hebona, another set of critics hold the view that *hebenon* is the correct reading and that it is a synonym of the well-known

henbane. There is a good deal of sound evidence that can be adduced in favor of this view. In the first place, metathesis of consonants is not at all an unusual phonetic phenomenon. Secondly, the argument advanced by some that hebenon is spelled with an "o" while henbane has an "a," is not a valid one because, according to Hanbury and Flückiger,[25] the writing *hennibone* for henbane is found in a vocabulary of the thirteenth century. Thirdly, the poisonous properties of hyoscyamus or henbane were known from the remotest antiquity and, furthermore, henbane was a common drug in Shakespeare's time. Fourthly, the poisonous properties of henbane are not infrequently mentioned in old English literature. Thus, Drayton in his Barons' Wars, p. 51, speaks of

> "The poisoning henbane and the mandrake dread."

And again

> "Here Henbane, Poppy, Hemlock here
> Procuring deadly sleeping."

Again in The Philosopher's Fourth Satire of Mars by Anton (1616), we find the following verse:

> "The poison'd henbane whose cold juice doth kill."

Fifthly, henbane is an official drug mentioned in old English pharmacopeias and dispensatories such as those by Dale and Salmon and others, and has been used from ancient times in the form of *ear drops*. Lastly, but not least in importance, and indeed of great significance, is the fact that Pliny describes toxic symptoms following instillation of henbane oil into the ear.

> "Oleum fit ex semine quod ipsum auribus infusum temptat mentem."[1]

Which means that the oil of hyoscyamus seeds instilled into the ears produces madness. It is to be noted that the very popular English translation of Pliny by Holland appeared in 1600. Inasmuch as the first quarto edition of Hamlet was probably written in 1600, though not published until 1603, Shakespeare undoubtedly must have been familiar with Holland's work and very probably might have had it in mind in issuing the later editions, and for that reason might have changed the reading of hebona to hebenon.

On the Toxicology of Hyoscyamus

The poisonous properties of hyoscyamus or henbane are too well known to be given here in detail. Henbane is certainly just as poisonous and in fact more poisonous than the yew-tree. Cases of poisoning with hyoscyamus are not at all uncommon and are described in the literature, ancient, medieval and modern. Detailed descriptions of such cases may be found in Blyth, Kobert, Kunkel, Peterson and Haines[26] and other text-books on toxicology. It is well to bear in mind, furthermore, that while *hyoscyamin*, the lethal dose of which is a little over one grain, is the principal constituent of hyoscyamus niger, the crude plant also contains variable quantities of the even more powerful alkaloids, *atropin* and *hyoscin* or scopolamin. The minimal lethal doses of hyoscin are even less than that of hyoscyamin. A strong extract of hyoscyamus would therefore be a very powerful poison.

Discussion

Whether hebona or yew-tree, or whether hebenon or henbane, is the correct reading in the passage before us will probably be never settled, nor will we venture to assert an opinion as to which drug or poison Shakespeare meant. Indeed, for the appreciation of Hamlet either reading may be chosen. As a pharmacologist, however, I cannot help surmising that both hebona and hebenon might have been written by Shakespeare himself. It would not be too far-fetched to suppose that the idea of a powerful poison was suggested to the author by the yew-tree on the one hand, while the unusual administration of it through the ears was suggested by henbane, on the other. Certainly the practice of instilling hyoscyamus into the ear was not unknown in Shakespeare's times, and the appearance of Holland's translation of Pliny just about the date of the first quarto edition of Hamlet lends further support to this view.

Much has been made of, by older writers, of Shakespeare's description of the effects of the poison as an argument for and against the yew or the henbane theory by the respective critics on the one side or the other. These arguments are amusing to the modern toxicologist, as we cannot say that the symptoms pictured in the passage before us are more applicable to the one poison than the other. Nor have we a right to expect the author to have known the detailed symptomatology produced by either. Three features are mentioned in connection with the hebona or hebenon poisoning which we are discussing. Firstly, Shakespeare speaks of the rapidity of the toxic effect:

> "Swift as quicksilver it courses through
> The natural gates and alleys of the body."

Secondly, reference is made to peculiar leprosy-like cutaneous manifestations of the poisonous effect:

> "A most instant tetter barck'd about
> Most lazar-like, with vile and loathsome crust
> All my smooth body."

Thirdly, mention is made as to the circulatory effect:

> "With a sudden vigour it doth posset
> And curd, like eager droppings into milk,
> The thin and wholesome blood."

It cannot be said that the yew-poisoning runs a more rapid course than that following hyoscyamus. Both are rapid in their action. Harrison quotes an old French writer as stating that the yew-tree gives rise to a characteristic cutaneous eruption and uses this point as a strong argument in favor of hebona, the yew. None of the modern authorities, however, describe any specific cutaneous lesions in connection with poisoning by *taxus baccata*. In fact, skin eruptions result perhaps more commonly after the giving of hyoscyamus and belladonna even in non-lethal doses. Lewin[27] describes erythema, urticaria, pustules, and even purpura occurring in sensitive persons after therapeutic doses of hyoscyamus preparations. Nor does modern toxicology and pharmacology show any specific

[1] Natural History, XXV, 17.

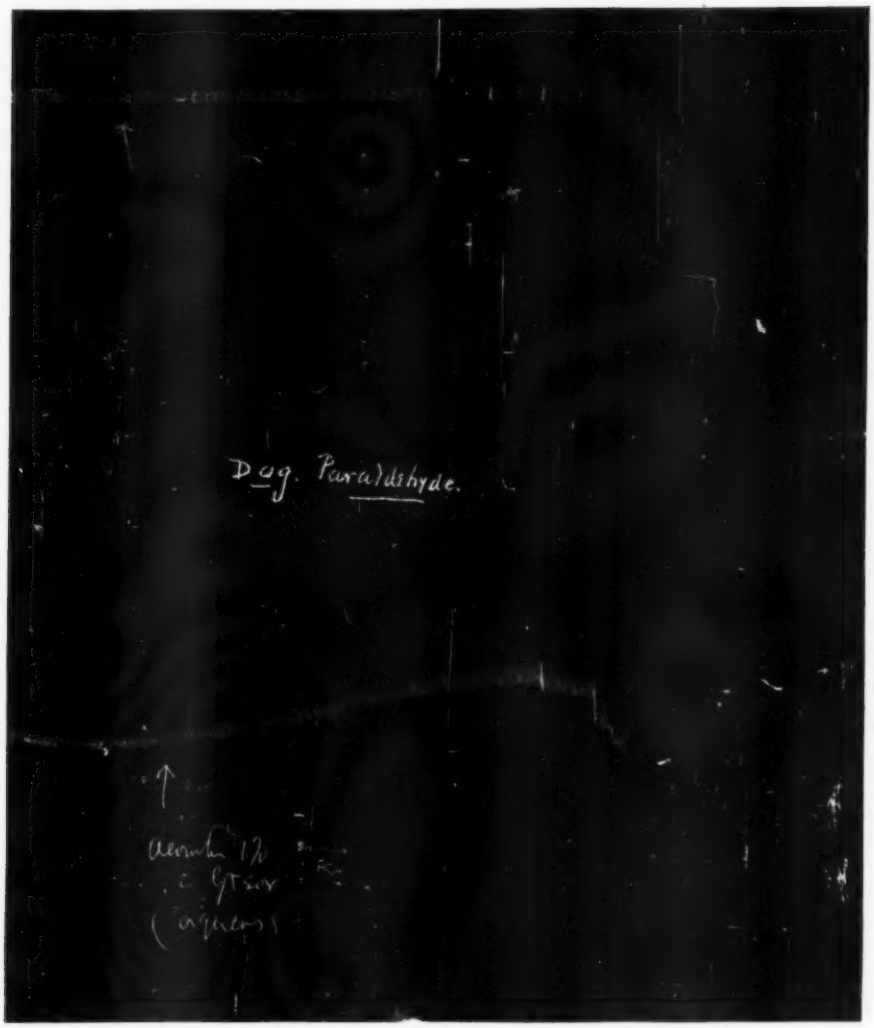

FIG. 1.—Dog. Paraldehyde Anesthesia. 1 per cent of Aqueous Solution of Aconitin HCl. in left ear. Showing effect on heart and respiration.

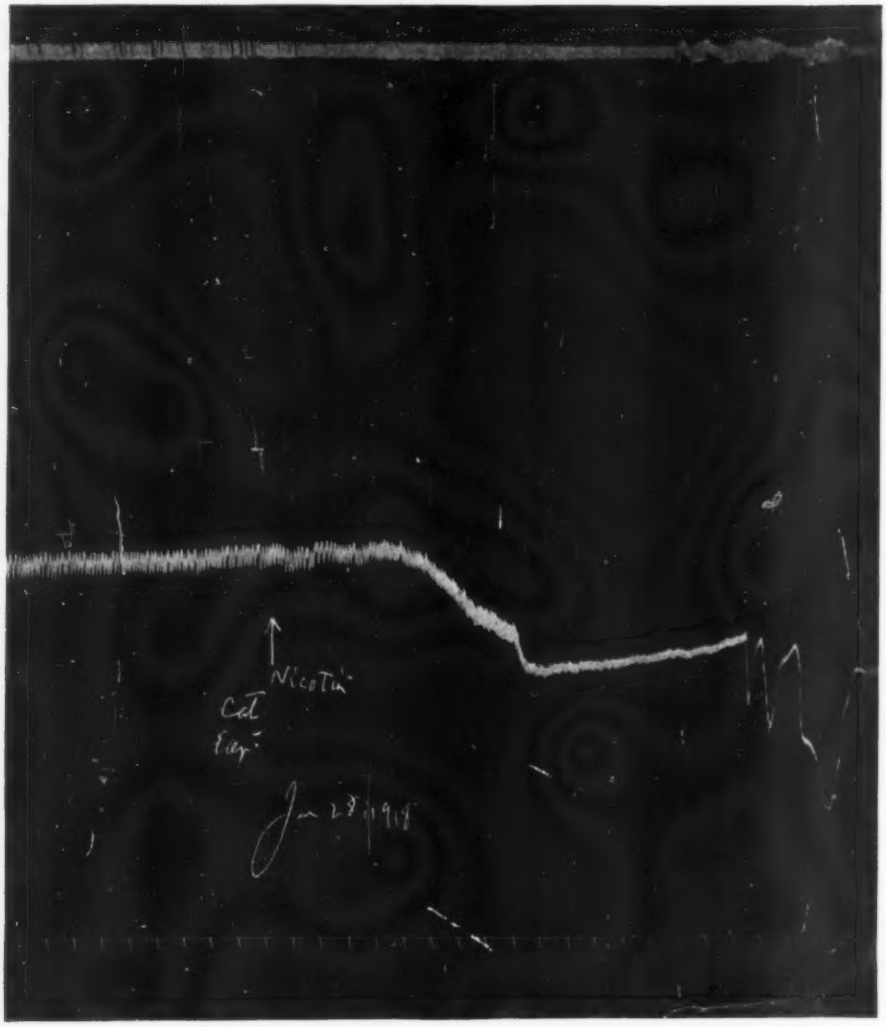

FIG. 2.—Cat. Urethane Anesthesia. A few drops of Nicotin instilled into the ear produce death in 15 minutes.

effect of toxin or hyoscyamin on the blood corpuscles or the plasma, so that Shakespeare's simile must be taken merely as a forcible poetic description of the rapid paralysis of respiration and circulation produced by the poison used.

On the Instillation of Poisons Into the Ear

The method of poisoning described in connection with the murder of Hamlet's father is unique and unusual. Although drugs were used in treatment of ear affections in ancient times, no reference is found of their instillation into the ears for homicidal purposes. The doubtful credit for such *finesse* in the administration of poisons must be ascribed to medieval experts and more particularly to the Italians and French. A character in one of the old plays says "Poison speaks Italian." It is well known that poisoning rose to the distinction of an art at that time in Italy and France. A perusal of fascinating books dealing with professional poisoning in the Middle Ages, such as those by Legué [22] or by Thompson [23] and others, will furnish astounding corroboration of this fact. One of the famous older works dealing with the art of poisoning is the *Magia Naturalis* or Natural Magic of the Italian de la Porta. This writer discusses various subjects, and in a chapter on cookery gives some delicious recipes for demoniacal concoctions calculated to produce unfailing results. The following example from de la Porta, quoted by Thompson, will serve as a good illustration of some of the poisonous concoctions used in his times.

Venenum Lupinum

> **"Take of powdered leaves of aconitum lycoctonum, taxus baccata, with powdered glass, caustic lime, sulphide of arsenic and bitter almonds; mix them with honey and make into pills the size of a hazelnut."**

That such experts in the art of poisoning should have thought of instilling poisons into the ear is therefore not surprising. We find several references to such a procedure in old English literature. The following is a quotation from Marlowe's Edward II, Act V, Scene 4:

> **"I learned in Naples how to poison flowers:**
> **To strangle with a lawn thrust down the throat;**
> **To pierce the windpipe with a needle's point;**
> **Or whilst one is asleep, to take a quill**
> **And blow a little powder in his ears:**
> **Or ope his mouth and pour quicksilver down."**

Another reference to poisoning through the ears is found in a later passage in Hamlet, Act III, Scene 2, in connection with the re-enactment of the murder by the players under the direction of Hamlet. Here we read:

> **"His name's Gonzago; the story is extant, and writ in choice Italian."**

A note in the Arden edition of Hamlet in connection with this passage says:

> **"In 1538 the Duke of Urbino married to a Gonzaga, was murdered by Luigi Gonzago, who dropped poison into his ear."**

One other case of poisoning through the ears, of especial interest to us as medical men, is mentioned by Robert [20] in his thesis on the Poisonings of the Middle Ages. It is well known that King Francis II of France died very suddenly; his death was supposed to have been due to poisoning, and the celebrated French surgeon, Ambroise Paré, was deliberately accused, of course without foundation, of having murdered the king by blowing a poisonous powder in his ear.

It is very interesting to note that the original Hamlet story has no mention of instillation of poison into the ear.[21] In the Hamlet story by Saxo Grammaticus, Hamlet's father is killed by his brother with a steel weapon. The instillation idea is original with Shakespeare and was probably suggested by the prevalence of the horrible form of homicide by poisons so common at the time and the toxic properties of the yew-tree and henbane which we have already discussed in detail.

On the Absorption of Drugs and Poisons Through the Intact Ear

In connection with Shakespeare's passage which we have just discussed in detail, an interesting scientific question arises as to whether drugs or poisons can be absorbed through the intact external ear canal and drum into the general circulation and produce constitutional symptoms. During the past year the author has been engaged in the study of absorption of drugs and poisons through unusual and unexpected channels, such as the eye,[24] the bladder, the urethra, the ureters, pelvis of the kidneys,[25] vagina,[26] etc. It was interesting, therefore, to inquire into and investigate experimentally the possibility of absorption of drugs through the ear. The results of these experiments will be published in detail in the *Journal of Pharmacology and Experimental Therapeutics*. It may be here stated that the author has found that a number of poisons can be and are absorbed through the intact ear.

The powerful alkaloid, aconitin, in the form of the hydrochloride, was found to be absorbed through the intact ears of animals even when introduced in an aqueous solution. Fig. 1 shows the characteristic effects of aconitin poisoning in a cat.

Equally rapidly and easily is absorbed through the ear the powerful volatile alkaloid nicotine. Fig. 2 illustrates the toxic action of this drug.

The question of absorption of belladonna and atropin was undertaken with especial interest in connection with Shakespeare's reference to henbane. It was found that atropin in an aqueous solution is not absorbed through the ear, but an alcoholic solution of the belladonna alkaloids in the form of a weak tincture gave positive experimental proof of the absorption of that drug as shown by the paralysis of the vagus terminals in the heart.

It is well known that a large number of drugs are introduced by physicians into the ears for medicinal purposes. Hyoscyamus in the form of an oil or a tincture has been long employed for the relief of earache; a compound tincture of hyoscyamus under the name of Balsamum tranquillans is official in several European pharmacopeias. In the light of

the experimental investigations just reported, such a use of hyoscyamus as an anodyne would certainly seem to be rational.

Another drug used in the treatment of ear affections with an intact drum is phenol or carbolic acid. A specialist tells me that he prescribes often in cases of middle-ear inflammation a few drops of a 5 per cent solution of carbolic acid in glycerin. I have found in experimenting on animals that such a solution of phenol in glycerin is absorbed through the ear, as evidenced by its effects on blood pressure. The use of carbolic acid in the treatment of ear affections, therefore, is on the one hand a rational one but on the other hand somewhat dangerous.

We cannot in this historical paper enter into a detailed account of the above experiments; they will be published in their proper place. Suffice it, however, to say that a number of drugs, and among them hyoscyamus or henbane, can be and are absorbed through the intact ear, and we may therefore conclude our appreciation of Shakespeare's passage from Hamlet which we have just been discussing, with saying that after all "Shakespeare was certainly right."

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ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin Prepared by the Authors

DUODENO-URETERAL FISTULA OF SPONTANEOUS ORIGIN

Report of Case

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(Abstract from the Journal A. M. A., 1918, LXX, 376)

(*From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital*)

The proximity of the duodenum to the right renal pedicle, and the danger of injury to the former during nephrectomy, have been pointed out by Dr. W. J. Mayo, who cites four cases of duodenal fistula following nephrectomy, the first three of which were fatal, the fourth being cured by transperitoneal closure of the duodenum. The case reported herewith is doubly interesting in that it further emphasizes this danger of duodenal injury during nephrectomy, and presents a most unusual (and apparently unique) condition, namely, a definite demonstrable fistula connecting duodenum and ureter, *which existed before any operative procedure had been carried out.*

The patient was a man of 29, complaining of extreme frequency of urination, urgency and bladder irritability; and giving a history of an obscure fever, associated with pain in the right flank, occurring four years before admission. It is possible that this was a perinephritic abscess.

The general physical examination was negative. The urine showed large numbers of pus cells, bacilli and cocci.

Ureteral catheterization, repeated twice at weekly intervals, showed normal urine from the left kidney, and from the right, came scanty amounts of cloudy fluid, distinctly green in color, the sediment from which was made up largely of an amorphous mucoid material, containing a few pus and epithelial cells, and an occasional bacillus. There was no urea content, and not a trace of phenolsulphonphthalein. The resemblance of this greenish fluid to bile was mentioned at the time, but this possibility was not seriously considered, nor were tests for bile carried out. The phenolsulphonphthalein output from the left side, during one-half hour, was 30 per cent. It was quite evident, therefore, that the right kidney was functionally dead.

The pyelogram (right) showed no gross abnormality of the pelvis. At the level of the upper border of the third lumbar vertebra, and at about the uretero-pelvic junction, there was visible a small nipple or diverticulum of thorium, projecting from the ureter for about 1 cm. in a direction that seemed to be upward, outward and backward, and apparently ending blindly. This suggested an incompletely filled bifid ureter.

Nephrectomy demonstrated a duodeno-ureteral fistula. After dense adhesions around the kidney had been freed, and the latter delivered, it was noted that a knuckle of duodenum

was pulled up, and was intimately associated with the mass of scar tissue which included ureter, pelvis and pedicle in an indistinguishable mass. In dissecting the duodenum free it was necessary to cut into the ureter and leave a small area of the wall of the latter attached to the duodenum. Since the opening was very small and surrounded by scar tissue, and since the patient's condition was not good, no attempt at duodenal closure was made.

Convalescence was uneventful excepting that there was discharge of duodenal content from the incision from the fourth to the twelfth day. The most striking feature was the immediate cessation of bladder symptoms. On the day following the operation the patient began voiding without pain and at normal intervals, for the first time in two and one-half years; a remarkable contrast to the extreme bladder irritability before operation.

A careful study of the literature fails to reveal any other case of duodeno-ureteral fistula. In addition to the cases of duodenal fistula following nephrectomy reported by Mayo, there is a somewhat similar case of Thévenard in which a duodenal fistula developed 10 years after nephrectomy in a persistent sinus, probably tuberculous, which had existed since nephrectomy, with intermittent abscess formation. Van Vranken has reported a case, in a man, aged 45, with a large abscess of obscure etiology, pointing over the left Poupart's ligament, which he drained, finding that the abscess cavity communicated with the descending colon. After a month of fecal drainage from the abscess cavity, urinary drainage also appeared and persisted for several weeks, the fistula finally healing completely, although the case was followed for only six months. This case, in which colon and ureter discharged into a common abscess cavity, is the only one to be found in the literature which is in any way analogous to the case reported above.

In view of the history of intermittent attacks of chills and fever, accompanied by pain in the right flank; of the evidence found at operation of an old inflammatory process involving the perirenal tissues; and, of the fact that the duodenum, excepting at one point, was normal in appearance and consistency, the most plausible explanation of the origin of the duodeno-ureteral fistula is that the latter was preceded by a perinephritic abscess, which went on to spontaneous cure by rupture into both duodenum and ureter. The condition cannot be explained as an embryologic defect on account of the diverse origins of duodenum and ureter, the former arising from entoderm, and the latter being an evagination from the Wolffian duct, which is derived from mesoderm. It was fortunate that during the operation a good exposure was obtained, because the knuckle of soft-walled duodenum, when pulled up alongside the dense scar tissue at the hilum, could not be palpated, and was discovered only by inspection. It might readily have been clamped and severed with the pedicle, particularly if the necessity for hastily controlling hemorrhage through an inadequate incision had arisen.

The most interesting feature was the immediate cessation of bladder symptoms on the day after operation; the over-night return to normal of a bladder which for two and a half years had been a constant source of distress. The only reasonable explanation is that the irritability was due to the constant presence of small amounts of duodenal content, and presumable trypsin, in the bladder.

Conclusions.—1. This case of duodeno-ureteral fistula is apparently unique.

2. In cases in which there is marked inflammatory reaction around the renal pedicle, the only safe procedure is to locate the duodenum before applying clamps.

URINARY ANTISEPSIS

A Study of the Antiseptic Properties and the Renal Excretion of Compounds related to Phenolsulphonphthalein: Preliminary Report

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(Abstract from the Journal A. M. A., 1918, LXX, 581)

(*From the James Buchanan Brady Urological Institute*)

The ideal internal urinary antiseptic must be a drug which is chemically stable, non-toxic and non-irritating to the urinary tract; which is antiseptic in high dilution (in urine, as well as in water) and which is eliminated unchanged in high percentage by the kidney. There is no such drug known. A consideration of the properties possessed by phenolsulphonphthalein, however, shows that this compound comes very close to filling all the above requirements. Phenolsulphonphthalein is chemically stable, non-toxic and non-irritating, and is eliminated by the kidney with almost incredible rapidity and completeness; but it has no antiseptic properties, excepting in water in its free acid form. (Clinically, it is used as the monosodium salt.) In view of these remarkable properties, it was thought worth while to attempt a modification of the phenolsulphonphthalein molecule, with the hope that an antiseptic compound might be produced which still retained the desirable qualities of the original drug. As the problem gradually increased in scope, it was found advisable to investigate a large number of compounds distantly related to phenolsulphonphthalein, as well as those closely related. The total number of compounds experimented with is at present about 195, the antiseptic properties of which will be enumerated in subsequent publications. This report includes only those drugs closely related to phenolsulphonphthalein.

Each compound was investigated with two objects in view; first, to determine the rate of elimination by the kidney, and second, to determine the antiseptic properties. Rabbits were used for determining renal elimination, the drug being injected intravenously (in 10 mg. amounts, in 1 per cent solution), the animals catheterized after one hour, and a colorimetric estimation of percentage of excretion made with the Hellige colorimeter.

It was necessary to carry on parallel antiseptic tests for each compound both in urine and water. As will be shown below, and in subsequent publications, there are numerous compounds which are germicidal in high dilution in water, but which lose this property entirely when diluted in urine, and

which even permit the growth of organisms in urine when in relatively strong concentration. This astonishing fact has proved to be a great obstacle, for antisepsis in urine becomes, therefore, quite a different problem from antisepsis in water.

The metallic salts of phenolsulphonphthalein (Na. Ag, Cu, Hg and Ba) were all discarded because they were either toxic to the animals or inert as antiseptics in urine.

Of the sulphonphthaleins listed in Table I, the only one to show antiseptic properties in urine (pyrocathechinsulphonphthalein) fails to be excreted. It will be noted that there are several other sulphonphthaleins which show the same marvelous "renal affinity" as does phenolsulphonphthalein.

Of the halogen derivatives of sulphonphthaleins investigated (tetrabromphenolsulphonphthalein, tetrachlorphenolsulphonphthalein, di-iodophenolsulphonphthalein, dibromcresolsulphonphthalein and di-bromthymolsulphonphthalein), all are inert in urine, and none but the tetrachlor compound is excreted.

The phthaleins (phenolphthalein, thymolphthalein, tetrabromtetrachlorphenolphthalein, tetra-iodophenolphthalein, phenoltetrachlorphthalein and sulphonated phenolphthalein) are likewise useless. The last-named compound is excreted, although its chemical structure is quite different from that of phenolsulphonphthalein.

The xanthones are characterized by the fact that two of the phenol groups are linked together by an oxygen atom, and they differ from the phthaleins only in this respect. Of the compounds of this class investigated (resorcinphthalein, resorcinsulphonphthalein, orcinsulphonphthalein, rhodamin and resorcinsaccharein), all, in solution, are greenish and extremely fluorescent, and without exception they are excreted by the kidney with a rapidity as great, if not greater, than that of phenolsulphonphthalein; the average rate of excretion for the group being 70 per cent in one hour. Since these compounds are all quite different chemically, but have one characteristic in common (the oxygen linking the two phenol groups), and since they all show great "renal affinity," it is reasonable to assume that we have here a definite relationship between chemical structure and physiological action. As germicidal agents, all the xanthones are inert excepting rhodamin, which comes very close to filling all the requirements. Rhodamin, which differs from resorcinphthalein (fluorescein) only in that the two hydroxyl groups are replaced by amino groups, is chemically stable and non-toxic, is very rapidly excreted, and kills the colon bacillus in one hour in a dilution of 1:2000, in water (10 times the strength of phenol); but when the compound is diluted *in urine* this property is entirely lost. An investigation of the nature of this interfering action in urine has not been completed.

Summary.—The property possessed by phenolsulphonphthalein, by virtue of which it is rapidly eliminated by the kidney, is by no means limited to this compound. Several other more or less closely related compounds show the same striking "renal affinity," and might also be of value in testing renal function were it not for the fact that phenolsulphonphthalein itself is so nearly ideal for the purpose.

Compounds of the xanthone class, that is, phthaleins (though not necessarily sulphonphthaleins) in which there is an oxygen atom linking the two phenol groups, show a similar remarkable "renal affinity."

The bromination of these compounds, both sulphonphthaleins and xanthones, interferes with their excretion.

In view of the hitherto overlooked fact that numerous actively germicidal compounds lose their strength (owing to an as yet unexplained cause) when simply diluted with urine in a test-tube, the value of every drug used for the purpose of urinary antisepsis ought to be questioned until its antiseptic strength *in urine* has been experimentally demonstrated.

Since it has been possible to demonstrate a certain relationship between chemical structure and renal excretion, and to predict, with a reasonable degree of accuracy, which drugs will and which will not be rapidly excreted; since the synthesis of germicidal compounds, very closely related to the types excreted, has been accomplished; and since one of these germicidal compounds (rhodamin) was excreted and would have been successful but for the interfering action of the urine, the problem has been shown to be worthy of further investigation. It is hoped that these experiments may call attention to the inadequacy of the urinary antiseptics in general use, and stimulate interest in the possibilities offered by synthetic chemistry.

TABLE I

THE EXCRETION AND THE ANTISEPTIC PROPERTIES OF THE SULPHONEPHTHALEINS

Name	Antiseptic strength				Excretion percentage after one hour
	In water		In urine		
	Kills in one hour	Fails in one hour	Inhibits Development	Permits Growth	
Phenolsulphonphthalein	.....	1:200	.....	1:200	70
Thymolsulphonphthalein	1:200	1:1,000	.....	1:200	Trace
Salicylsulphonphthalein	.....	1:200	.....	1:200	Trace
Hydrochinonsulphonphthalein	.....	1:200	.....	1:200	40
Cresolsulphonphthalein	....	1:200	.....	1:200	70
Tetra-aminophenolsulphonphthalein	1:200	1:1,000	1:200	1:500	0
Alphanaphtholsulphonphthalein	1:200	1:1,000	.....	1:200	Unstable
Orcinsulphonphthalein	.....	1:200	.....	1:200	70
Pyrocatechinsulphonphthalein	1:2,000	1:5,000	1:1,000	1:2,000	0
Tetranitrophensulphonphthalein	.....	1:200	.....	1:200	Hemoglobinuria
Guaiacolsulphonphthalein	1:200	1:1,000	.....	1:200	Trace
Resorcinsulphonphthalein	.....	1:200	.....	1:200	75
Pyrogallolsulphonphthalein	.....	1:200	.....	1:200	30
Phenol	1:180	1:220	1:900	1:1,000	

LES NEPHRITES DE GUERRE

By P. Ameuille

(Revue de pathologie de guerre, No. 5. Vigot, Editeur. The full Article to appear in Journal of Urology, translated from the French by H. O. Mosenthal)

Etiology.—It is certain that nephritis is much more common under present conditions at the fighting front, than during times of peace. The disease occurs among soldiers after they have engaged in military operations for about six months. It is more common among the English troops than among the French. The higher protein consumption of the former may have a bearing in this connection. The Hindoo contingent and the officers of the other forces are not subject to the disease. It is found almost entirely among the men who live in the

trenches and those who are engaged in constructing them. It appears to be certain that exposure to cold is not the exciting cause, since nephritis is as prevalent in the warmer seasons as it is during the colder months. It is tempting to assume that the disease is the result of a bacterial infection, though at the present time proof of this contention is lacking. War nephritis is not a complication of any of the usual infectious diseases—diphtheria, scarlet fever, syphilis and others, but is a disease entity.

PATHOLOGY.—The kidneys may look normal on gross as well as on microscopical examination. Usually the kidneys are larger than normal and have a milky white or mottled appearance. In the interstitial tissue there are evidences of congestion, edema and exudation. The last is made up largely of polymorphonuclear cells, and may be said to be characteristic of war nephritis, since it has previously been found only on rare occasions. These inflammatory foci, if large enough, assume the appearance of the conventional miliary tubercle to the naked eye, and may be mistaken for it. They may invade the tubules and fill them; otherwise they are intact. The glomeruli are usually not involved, although in some of the later stages of the disease Andrewes has reported a proliferation of the epithelium of Bowman's capsule, followed by a gradual obliteration of the glomerular tuft. In the liver and heart the same characteristic inflammatory nodules, which have been described in the kidneys, are found. Bronchopneumonia is nearly always present. Particular stress is laid on the fact that there are lesions in organs other than the kidneys, especially the heart and the liver, and that there are characteristic inflammatory foci made up largely of polynuclear cells.

CLINICAL TYPES.—*Acute Nephritis with Edema.*—This is the predominant type, constituting 90 per cent of the author's cases. At the onset there is a short febrile period, usually accompanied by general malaise; there may be dyspnea on exertion, even paroxysmal dyspnea; hematuria and albuminuria are often noted; edema, especially of the face, is generally the first symptom. All of these cases, for a short period at least, give evidence of an increased blood urea. The urinary signs and the characteristics of the edema are much like those we have been accustomed to deal with in acute nephritis with edema. In the urine there are polymorphonuclear cells which may have some relation to the characteristic inflammation described under pathology. The cases vary in intensity from those which are very mild, and in which the patients have only transient edema so that the disease may go unrecognized, to those which are very severe and are characterized by a persistence of the signs of nephritis, notably, albuminuria, recurrent edema, arterial hypertension, and impaired ability to excrete urea.

Acute Azotemic Nephritis.—This may escape observation, inasmuch as there may be no albuminuria and the blood urea is frequently not determined. No attention is paid to this type in any but the French literature. There is usually a marked fever, an albuminuria, which may or may not be accompanied by a hematuria, and—the constant and characteristic feature—a high blood-urea. When the nephritic symptoms are not in evidence, as is usually the case, the author speaks of the condition as a *masked acute azotemic nephritis.* These patients are often thought to have "fever," "gastric fever," bronchitis, bronchopneumonia, etc. Headache, epileptiform seizures, delirium and asthma may divert attention to the nervous system, when in reality it is the nephritis with the resulting increase in the blood-urea which is responsible for these signs. At times jaundice is present. In this *acute azotemic nephritis with jaundice* renal lesions are found at autopsy, the blood-urea is high and the spirochæta icterohemorrhagiæ is supposed to be the cause.

TREATMENT.—In the early stages no solid food is given and fluids are forced. While there is an azotemia the diet should consist exclusively of milk. When the azotemia disappears, no restrictions in the diet, except as regards salt, are necessary. In conjunction with the salt restriction, theobromine (up to 5 gm. a day, though more than 3 gm. is often poorly tolerated) may be used. After apparent recovery, the ability to excrete urea should be measured by Ambard's Coefficient, and the protein of the diet regulated accordingly.

PROGNOSIS.—The immediate prognosis in acute azotemic nephritis is not so good as in the edematous type. The persistence or increase of a blood-urea is of more significance in this regard than the actual height of the azotemia at the onset of the disease. However, when recovery does take place, it is more rapid than in the edematous type and it is usually complete. The acute nephritis with edema usually has a comparatively prolonged course, but the mortality is negligible. A cure within two or three weeks is the exception. Concerning the ultimate prognosis of these cases, there is no information at hand at present. It is known that some of the patients for an indefinite period may exhibit a tendency to edema, a diminished ability to excrete urea (according to Ambard's Coefficient) and occasionally arterial hypertension.

ON A CASE OF CHILDHOOD CONFLICTS WITH PROMINENT REFERENCE TO THE URINARY SYSTEM; WITH SOME GENERAL CONSIDERATIONS ON URINARY SYMPTOMS IN THE PSYCHONEUROSES AND PSYCHOSES

By C. MACFIE CAMPBELL, M. D.

(Abstract from the Psychoanalytic Review, 1918)

The report of a case of a seven-year-old girl who was studied at the dispensary of the Phipps Psychiatric Clinic for four years. The girl showed difficult behavior at home and at school, and made a superficial impression of being mentally defective; whereas, in reality, she was quite intelligent and very alert. She asked questions to an obsessive degree; this seemed to indicate an intense curiosity as to some special topic which did not dare to seek direct satisfaction. An unusual interest in water seemed to express the child's interest in her own urinary apparatus; her marked absorption in this topic was accompanied by certain peculiarities in relation to urination. The child was brought up in a very repressive home atmosphere, and had indulged in erotic games and ruminations; these erotic interests and activities were referred to quite

openly by the child at the end of the four years, and the rôle of these conflicts in causing the child's abnormal conduct was made clear.

The case illustrates in an unusually convincing way certain mechanisms which frequently are not realized, or at least are not so frankly admitted, by the child; there was no necessity in this case for any such subtle interpretation as that which detracts from the value of some well-known cases in the literature (cases of Freud, Jung).

The influence on the urinary mechanism of sexual factors is important not only in such disorders of the child as enuresis, but also in the psychoneuroses of the adult; this influence is at the basis of many otherwise obscure cases of dysuria and retention.

The situation is illustrated by brief references to a few cases in which the patient was treated for supposed tuberculosis of the spine, cystitis, etc., while the real trouble lay in the underlying difficulty of assimilation of the instinctive life.

NOTES ON NEW BOOKS.

Ourselves—A Personal and Family History Register for Preserving Records of a Private and Personal Nature, for One Married Couple and Their Children. By JOHN MADISON TAYLOR, A. B., M. D. (*Philadelphia: F. A. Davis Company, 1917.*)

Years ago Francis Galton prepared an outline for family histories suitable for studies of heredity. It has long been out of print, and Dr. Taylor now provides a family book with directions for examination and blanks which no doubt will serve the purpose of recording a great deal of valuable information which cannot be trusted to memory. The book contains registers for the ancestors of father and ancestors of mother (to the 7th generation) and accompanying diagrams; pages for the personal histories of health of individuals over one year of age and blanks for phenomena of an attack of illness, injury, or operation; blanks for baby records—brief memoranda of circumstances of birth, growth, development, etc., physical and mental, up to one year; tables of standard weights and heights and circumference of head and chest; charts for recording weight and height; blanks for observations and findings of specialists in eye, ear, throat, and nose; blanks for clinical laboratory findings, urine, feces, blood, etc.; anatomical diagrams, to record site, size and character of lesions, deformities, etc.; diagrams for findings of dental surgeons—development, condition, repairs made, etc., of teeth; pages for special happenings—noteworthy incidents, education, tastes, distinctions, etc., all facts bearing on the evolution of personality and character; pages for photographs, at different ages, with dates; pages for handwriting, at different ages, with dates. In the appendix there are 11 chapters treating of the development of body, mind, character, and personality: The child as a problem for parents and others. The building of a citizen. How far can improved conditions of life overcome inherited tendencies? Personal hygiene. Hints and warnings in the bringing up of children, etc. A. M.

The Elements of the Science of Nutrition. By GRAHAM LUSK, PH. D., SC. D., F. R. S. (Edin.). Third Edition, Reset. Cloth $4.50. (*Philadelphia and London: W. B. Saunders Company, 1917.*)

The third edition of this well-known book needs no introduction to the workers interested in nutrition, whether they be physiologists, chemists or physicians. Ever since the appearance of the first edition of this work in 1916, it has justly been looked upon as the authority in its field. It has served to link together the pure science of the psychological and pathological chemist and the science of the pathologist with that of the clinician. This has been an enormous task and one which has never been so successfully performed. Professor Lusk has, in the previous editions, exhibited rare judgment and critical skill in culling the most useful and trustworthy theories and experimental results from the ever-accumulating mass of literature. The present edition is considerably larger than its predecessor, and its value has developed in direct proportion to its size. The presentation is in the same clear, simple and forceful style as previously. Professor Lusk has accomplished much for medical science by his own efforts in research and by his generous encouragement and supervision of the men associated with him. The book under consideration may be looked on as an epitome of the author's unbiased impressions, and is to be valued correspondingly. The only regret which the reader experiences in reviewing this volume is to note that "the writer desires to state that he has no intention of again revising this book." It is to be hoped that in the combined interests of physiology, chemistry and clinical medicine, Professor Lusk may reconsider his decision.

A Dietary Computer. By AMY ELIZABETH POPE. Cloth $1.25. (*New York and London: G. P. Putnam's Sons, The Knickerbocker Press, 1917.*)

This book presents a series of tables of the composition and caloric value of foods, of carbohydrate equivalents and of recipes in a very acceptable form. The tabulations, as stated in the preface, are practical and easy to use.

Life of Dr. Lyman Spalding. By DR. JAMES ALFRED SPALDING. (*Boston: W. M. Leonard, 1916.*)

This book possesses much interest to all who are fond of medical biographies. It portrays very fully the life history of Dr. Lyman Spalding, a contemporary of Nathan Smith, Benjamin Waterhouse, George C. Shattuck, Caspar Wistar, Philip Syng Physic, John C. Warren, and other well-known medical men. Spalding obtained his medical education in the office of a preceptor, and had two brief courses of lectures at Harvard, where he received his degree. He practised medicine in a country town in New Hampshire at first, and taught chemistry for several weeks each year in the newly established medical school at Dartmouth College. He subsequently removed to Portsmouth, where he became interested in the extension of vaccination as a remedy for smallpox, and was a physician for a number of years. He was also a deft and able surgeon, and even operated for cataract. He prepared for many years "Bills of Mortality," giving the causes of death in the region of Portsmouth, and held the post of contract army surgeon to the troops in the vicinity.

He became later a lecturer in the newly established Fairfield Medical School in Eastern New York, and subsequently president of the same for several years. He taught anatomy, surgery and general medicine, and seems to have been an active-minded teacher with a genius for teaching. He spent a winter in Philadelphia, and there showed himself a deft anatomist. He made many anatomical preparations which were highly thought of. He removed subsequently to New York City, and while there originated and carried to successful completion a scheme for the preparation and publication of a National Pharmacopœia, and through his energy and persistence was able to devise a method of publication which has existed for the past century. He died in 1821 as the result of an accident.

The book has been prepared by Dr. James Alfred Spalding, his grandson, and is interesting throughout. A few letters written by Dr. Spalding and many letters written to him indicate the scope of his researches, and the interest felt in his work by eminent men in America and Europe. The preparation of the biography has involved great labor on the part of the author. The story, as he tells it, is of great interest and importance to all physicians and medical students. H.

Recollections of a New York Surgeon. By ARPAD G. GERSTER, M. D. (*New York: Paul B. Hoeber, 1917.*)

This handsomely-printed volume of nearly 350 pages gives an interesting autobiographical sketch of a well-known New York surgeon, born in Hungary in 1848, educated in Vienna, and transferred to New York in 1874, where he has since lived. The author relates his early experience in Brooklyn, his larger activities after he removed to New York City, his struggles and his successes. He held important positions in connection with various hospitals, notably the German, Mt. Sinai and Polyclinic Hospitals of New York, and has done excellent work as a teacher of surgery. His reminiscences of his early life in Hungary, of his student days in Vienna, and of his early experiences as a physician in general practice in America are interestingly told. He lets us also into the inner recesses of his occupations, amusements and recreations of his later years, and gives a charming view of his manner of growing old gracefully. He has been interested in sketching, literature, music and etching, out-of-door sports, travel and camping. The volume is a distinct contribution to intimate medical biography, and is full of interest and instruction to all physicians.

H. M. H.

The Respiratory Exchange of Animals and Man. By AUGUST KROGH, PH. D. Boards $1.80. (*London: Longmans, Green & Co., 1916.*)

Dr. Krogh has given in this book an excellent outline of the subject of respiratory exchange, stating the fundamental problems and reviewing the work done. The criticism of the literature, methods, results and conclusions are very pertinent and clearly written by a master of the subject. It is to be regretted that the book could not have been made larger, so that the various subjects could have been treated more at length, for in places there is little more than an encyclopedic recital of author and facts. The book is to be recommended to anyone who is working on or interested in gaseous exchange. H. L. H.

BOOKS RECEIVED

A Clinical Treatise on Diseases of the Heart. For the General Practitioner. By Edward E. Cornwall, Ph. B., M. D. 1917. 8°., 127 pages. Rebman Company, 1917.

Diseases of the Skin; Their Pathology and Treatment. By Milton B. Hartzell, A. M., M. D., LL. D. 51 colored plates and 242 cuts in text. 1917. 8°. 753 pages. J. B. Lippincott Company, Philadelphia and London.

Birth Fractures and Epiphyseal Dislocations. By Edward D. Truesdell, M. D. 1917. 4°. 135 pages. Paul B. Hoeber, New York.

The Thyroid Gland in Health and Disease. By Robert McCarrison, M. D. (R. U. I.), D. Sc. (Belf.), F. R. C. P. (Lond.). 1917. 8°. 286 pages. William Wood & Company, New York.

United States Public Health Service. Annual Report of the Surgeon General for the Fiscal Year 1917. 8°. 387 pages. Government Printing Office, Washington.

The Surgical Clinics of Chicago. Vol. I, No. 6, December, 1917. 8°. W. B. Saunders Company, Philadelphia and London.

The Medical Clinics of North America. Vol. I, No. 3, November, 1917. 8°. W. B. Saunders Company, Philadelphia and London.

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War Surgery of the Nervous System. A Digest of the Important Medical Journals and Books Published during the European War. Compiled by the Division of Brain Surgery, Section of Surgery of the Head. Office of the Surgeon General, War Department, Washington, D. C. 1917. 8°. 360 pages. Government Printing Office, Washington.

Interstate Commerce Commission. Thirty-first Annual Report. 1917. 8°. 213 pages. Government Printing Office, Washington.

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Manual of Medicine. By Thomas Kirkpatrick Monro, M. A., M. D. Fourth Edition. 1917. 8°. 1045 pages. C. V. Mosby Company, St. Louis.

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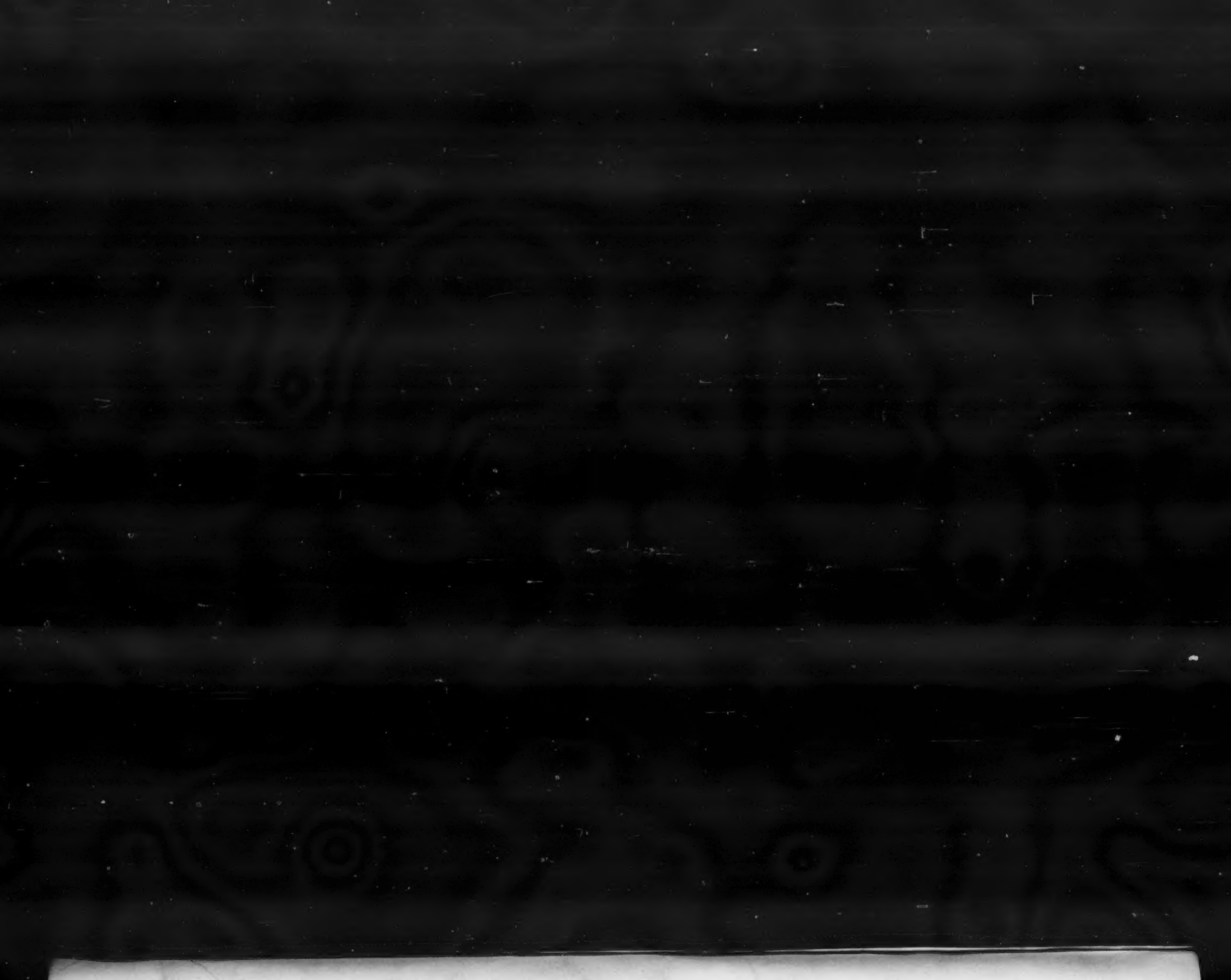
The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.